FACILE SYNTHETIC ROUTES TO FUNCTIONALIZED NITROGEN AND OXYGEN HETEROCYCLES VIA ZWITTERION ANNULATIONS

Thesis

Submitted in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

By

RASMI BHASKARAN P

Register No. 165028CY16F04

DEPARTMENT OF CHEMISTRY

NATIONAL INSTITUTE OF TECHNOLOGY KARNATAKA,

SURATHKAL, MANGALURU – 575025

January 2022

FACILE SYNTHETIC ROUTES TO FUNCTIONALIZED NITROGEN AND OXYGEN HETEROCYCLES VIA ZWITTERION ANNULATIONS

Thesis

Submitted in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

By

RASMI BHASKARAN P

Register No. 165028CY16F04

Under the guidance of

Dr Beneesh P B

DEPARTMENT OF CHEMISTRY

NATIONAL INSTITUTE OF TECHNOLOGY KARNATAKA,

SURATHKAL, MANGALURU – 575025

January 2022

DECLARATION

By the Ph.D. Research Scholar

I hereby declare that the Research Thesis entitled "**FACILE SYNTHETIC ROUTES TO FUNCTIONALIZED NITROGEN AND OXYGEN HETEROCYCLES VIA ZWITTERION ANNULATIONS**" which is being submitted to the **National Institute of Technology Karnataka, Surathkal,** in partial fulfillment of the requirements for the award of the Degree of **Doctor of Philosophy in Chemistry** is a *bonafide report of the research work carried out by me*. The material contained in this Research Synopsis has not been submitted to any University or Institution for the award of any degree.

RASMI BHASKARAN P

Register No. 165028CY16F04

Department of Chemistry

Place: NITK, Surathkal

Date: 14/06/2022

CERTIFICATE

This is to *certify* that the Research Thesis entitled "**FACILE SYNTHETIC ROUTES TO FUNCTIONALIZED NITROGEN AND OXYGEN HETEROCYCLES VIA ZWITTERION ANNULATIONS**" submitted by **Ms. Rasmi Bhaskaran P** (Register No: 165028CY16F04) as the record of the research work carried out by her, is *accepted as the Research Thesis submission* in partial fulfillment of the requirements for the award of the degree of ***Doctor of Philosophy***.

Dr. Beneesh P. B.
Research Guide
Assistant Professor
Department of Chemistry
NITK Surathkal - 575025
Date: 14/06/2022

Chairman – DRPC
Date: 14/06/2022

HEAD, DEPARTMENT OF CHEMISTRY
National Institute of Technology Karnataka
Surathkal, Srinivasnagar
MANGALORE- 575 025, D.K.

Dedicated to my parents….

ACKNOWLEDGMENTS

It is my great pleasure to express my gratitude to all those who have supported me throughout this journey.

I am incredibly grateful to my research supervisor, Dr. Beneesh P. B., Assistant Professor, Department of Chemistry, NITK Surathkal, for giving me this excellent opportunity to work under his supervision. It is my privilege to be the student of such a compassionate human being, and I cannot begin to express my thanks for his guidance, patience, motivation, and constant support. I also would like to express my gratitude to his family for their love and care towards me.

I would like to thank my Research Progress Assessment Committee members, Prof. B. Ramachandra Bhat, Department of Chemistry, NITK, and Dr. Saumen Mandal, Department of Metallurgical and Materials Engineering, NITK for their constructive and timely evaluation and thoughtful suggestions during the progress of my work.

I express my sincere thanks to NITK Surathkal for providing the laboratory facilities and research fellowship. I gratefully acknowledge CIF Manipal, SAIF, CUSAT, NIIST Trivandrum, and Mangalore University for the analytical and spectral data.

I must also thank the present Head of the Department, Dr. Udaya Kumar D., and the former Head of the Department, Dr. Arun M. Isloor, for all the support they have given me. I am grateful to all the Chemistry Department faculty members of NITK Surathkal for their encouragement and motivation during my Ph.D. programme. I am also indebted to the non-teaching staff of the department for their endless support for my day-to-day activities in the department.

I sincerely thank my research labmates Mr. Kalinganayak S. H. and Ms. Sreelekha K. M., for their warm friendship and unlimited support.

I would also like to extend my gratitude to Dr. V. K. Praveen, Senior Scientist at CSIR-NIIST, Thiruvananthapuram, Dr. Jith C. Janardhanan.

I am fortunate to have many friends and well-wishers in my life. I thank Mr. Nagaraj K., Ms. Neethu Raveendran, M., and Ms. Nivedha Vinod, who has always been there for me to provide constant mental support. My sincere thanks also go to all other research scholars and friends around NITK who supported me during my research life.

I want to express my sincere thanks to my beloved seniors, Dr. Viprabha K and Dr. Sunil Kumar from the Department of Chemistry, Dr. Manjusha Mahipalan, Dr. Manju M. S., and Ms. Rajani K. V. from other departments for their motivation, help, and support on various occasions.

I express my profound love and gratitude to my best friends Krishnapriya K. C, Anuroshith T. P, and Aswin I.V for their ever cherishing friendship and support which helped me overcome many hard times. I thank all my other friends for being there as a source of motivation and encouragement.

No words can be enough to acknowledge my family's encouragement and support. I owe my love and gratitude to them for their unconditional love, trust in me, and whole-hearted support during every stage of my life.

Many thanks to all those who have made this happen.

Rasmi Bhaskaran P.

ABSTRACT

Organic chemists are always interested in synthesizing diverse heterocyclic molecules using novel and straightforward techniques. The current research study comprises simple, efficient, and unique methodologies for constructing various nitrogen and oxygen heterocycles via zwitterion annulations.

A metal-free pyrazole and chromenopyrazole synthesis were developed using N- aryl hydrazones and acetylenic esters. Its applicability to various hydrazones, symmetric and unsymmetric alkynes, and acetylenic ketones were demonstrated. From the results drawn from the metal-free reaction of hydrazones and acetylenic esters, we speculated the possibility of a one-pot route for synthesizing pyrazole based on hydrazone and activated alkenes. The reaction between hydrazones and various activated alkenes in an acidic medium was examined to expedite the 1, 3-dipolar cycloaddition reaction. An efficient and improved method has been established for direct access to 4H-benzo[d][1,3]dioxin-4-one derivatives. A CuI-mediated addition of salicylic acid and acetylenic esters in a basic medium is followed by intramolecular cyclization in this approach. Interestingly, the benzodioxinone derivatives were transformed into salicylamides by treating the 4H benzo[d][1,3]dioxin-4-one derivatives with primary amines at room temperature.

The substrate scope of each reaction was studied by executing the reactions with variously substituted starting materials, and the characterization of the compounds using FTIR, ^{1}H NMR, ^{13}C NMR, HR-MS/LCMS, and SCXRD technique studies validated the structure of the final compounds.

Key Words: Zwitterion, Chromenone, Heterocycles, Hydrazone, Polycyles, Pyrazole, Dihydropyrazole, Benzodioxinone, Acetylenic esters, Activated alkenes

CONTENTS

LIST OF ABBREVIATIONS

^{13}C NMR	Carbon 13 nuclear magnetic resonance
1, 2- DCE	1, 2- Dichloroethane
1D-NMR	One dimensional nuclear magnetic resonance spectroscopy
^{1}H NMR	Proton nuclear magnetic resonance
2D-NMR	Two-dimensional nuclear magnetic resonance spectroscopy
2CzCP	8-(9*H*-[3,9'-bicarbazol]-9-yl)-3-methyl-1-phenylchromeno[4,3-c]pyrazol-4(1*H*)-one
$^{n}Bu_3P$	Tri-n-butylphosphine
t-BuOH	tert-Butyl alcohol
CAN	Ceric ammonium nitrate
CH_2Cl_2	Dichloromethane
CIE	Commission Internationale de l'Elcairage
COX	Cyclooxygenase
CNS	Central nervous system
$Cu(OAc)_2$	Copper (II) acetate
CzCP	8-(9*H*carbazol- 9-yl)-3-methyl-1-phenylchromeno[4,3-c]pyrazol-4(1*H*)-one
DAN	diaza-Nazarov cyclization
[Dbbta]Br	1,3-dibutyl-1H-benzo[d]- [1,2,3]triazol-3-ium bromide
DCM	Dichloromethane
DMAD	Dimethyl acetylenedicarboxylate
DFT	Density-functional theory
DME	Dimethyl ether
EtOH	Ethanol
equiv.	Equivalent
$Fe(acac)_2$	Iron(II) acetylacetonate
FT-IR	Fourier-transform infrared spectroscopy
HCT-116	human colorectal carcinoma cell
HOMO	Highest occupied molecular orbital
HRMS	High resolution mass spectrometry

h-TNAP	human tissue non-specific alkaline phosphatase
IAIDC	azomethine imine 1, 3-dipolar cycloaddition
IAP	tissue-specific intestinal alkaline phosphatase
IL	Ionic liquid
K_2CO_3	Potassium carbonate
KOH	Potassium hydroxide
$La(OTf)_3$	Lanthanum(III) trifluoromethanesulfonate
LUMO	Lowest unoccupied molecular orbital
MCR	Multicomponent reactions
MeOH	Methanol
$NaBH_4$	Sodium borohydride
NaH	Sodium hydride
$NaHCO_3$	Sodium bicarbonate
NaOH	Sodium hydroxide
Na_2CO_3	Sodium carbonate
Na_2SO_4	Sodium sulphate
$NbCl_5$	Niobium(V) chloride
NHC	N- heterocyclic carbene
NLO	Nonlinear optical
NSAID	Nonsteroidal anti-inflammatory drugs
OLED	Organic light emitting diode
PASS	Prediction of Activity Spectra for Substances
pet ether	Petroleum ether
PI3K	phosphoinositide 3-kinase
ROS	Reactive oxygen species
SCXRD	Single crystal X-ray diffraction
SO_2CF_3	Triflone
TADF	Thermally Activated Delayed Fluorescence
TBHP	tert-Butyl hydroperoxide
TD-DFT	Time-dependent density-functional theory
TFAA	Trifluoroacetic anhydride

TFA	Trifluoroacetic acid
TfOH	Triflicacid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
UV-vis	Ultraviolet–visible spectroscopy

SYMBOLS AND UNITS

%	Percent
°C	Degree Celsius
Al	Aluminium
C	Carbon
Cl	Chlorine
Cu	Copper
Cr	Chromium
Eu	Europium
Fe	Iron
g	Gram
Gd	Gadolinium
h	Hours
Hz	Hertz
M	Molar
m/z	Mass to charge ratio
MHz	Megahertz
min	Minutes
mL	Millilitre
mmol	Millimole
N	Nitrogen
Ni	Nickel
O	Oxygen
P	Phosphorus
Pd	Palladium

ppm	Parts per million
S	Sulphur
sec	Seconds
α	Alpha
β	Beta
γ	Gamma
δ	Delta

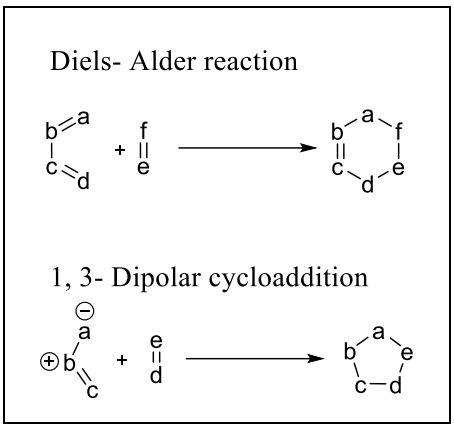
CHAPTER 1

INTRODUCTION: DIPOLAR CYCLOADDITION REACTIONS AND OXA-MICHAEL ADDITION REACTIONS - AN OVERVIEW

Abstract

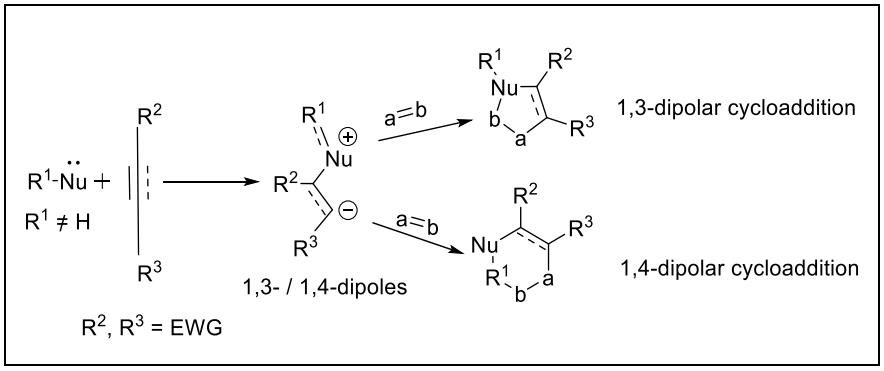
This chapter briefly introduces dipolar cycloaddition reactions and oxa-Michael addition reactions. The session is followed by a detailed literature survey on various synthetic methodologies towards the synthesis of pyrazoles, chromenopyrazoles and benzodioxinones. Further, the scope and objectives of the present work and the thesis framework is also described.

In organic chemistry, carbon-heteroatom bond-forming reactions are crucial as they provide viable routes for constructing heterocyclic frameworks. Among the many methods for forming carbon-heteroatom bonds, dipolar cycloaddition reactions stand out for their ability to produce complex heterocycles with biologically significant properties. Most organic reactions are multi-step processes involving intermediates, polar transition states, or free radicals in their reaction mechanisms. However, when conventional probes for studying mechanisms are used, some reactions show no evidence of involving intermediates. In general, cycloaddition reactions are concerted processes in which two new σ bonds are formed simultaneously via a cyclic transition state. These reactions have proven to be an effective method for creating cyclic systems. Buchner's discovery of 1, 3-dipolar cycloadditions in 1888 might be considered as the beginning of the field (Buchner 1888). Buchner, Beckmann (Beckmann 1890), Werner, Buss (Houk et al. 1995), and others made significant contributions in subsequent years. On the other hand, Huisgen recognized the generality of these reactions and developed a conceptual framework and the mechanistic information for 1, 3-dipolar cycloadditions in 1963 (Huisgen 1968, 2002; Huisgen et al. 1967). Huisgen's substantial experimental results led to significant advancement in the field of 1, 3-dipolar cycloadditions. The effects were most noticeable in the field of heterocyclic synthesis. The various types of cycloadditions include (2+2), (4+2), (1+3), and so on. Diels-Alder reaction [4 + 2] π, which is widely utilized in the stereospecific building of 6-membered ring systems, and 1, 3-dipolar cycloaddition [3 + 2], which is widely used in the stereospecific construction of 5-membered ring systems, are the most explored cycloaddition reactions (**Scheme 1.1**).



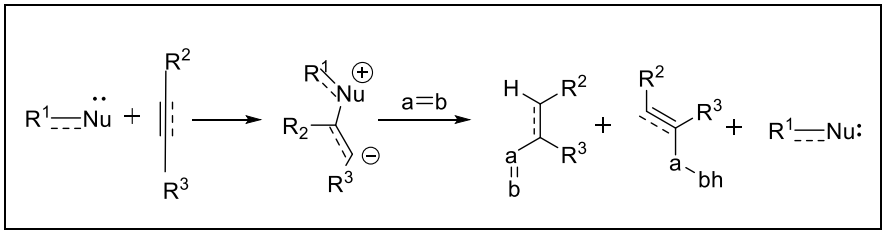
Scheme 1.1

Conventional dipoles such as 1, 3-dipoles, and 1, 4-dipoles represent a particular class of transient zwitterions. Generation of dipolar zwitterions occurs by adding a nucleophile to an activated π system. Depending upon the nature of the nucleophile, the zwitterion formed can be either 1, 3-dipole, or 1, 4-dipole. The nucleophiles are finally retained in the cycloaddition products.



Scheme 1.2 Generation of transient zwitterions

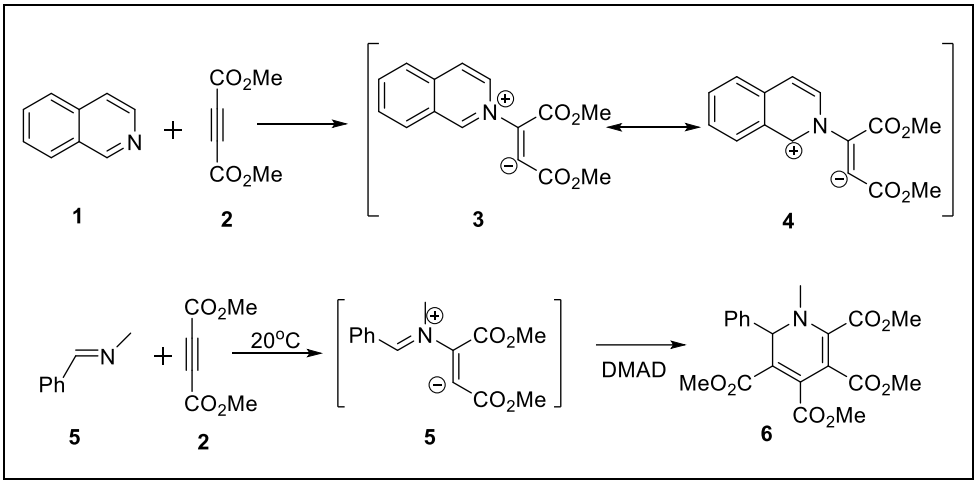
In some other zwitterion-mediated reactions, nucleophile plays the role of a catalyst. The nucleophiles initiate the reaction and finally get detached from the product.



Scheme 1.3

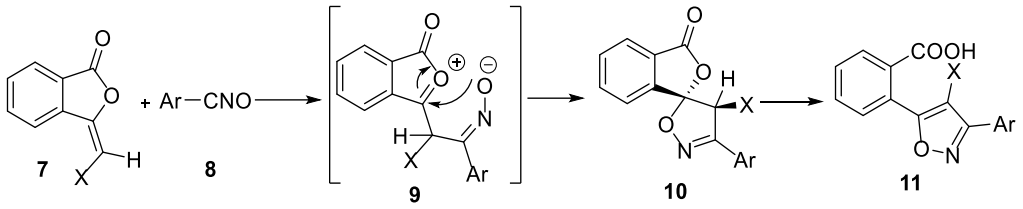
1.1. 1, 4- DIPOLAR CYCLOADDITION REACTIONS

A six-membered heterocycle is usually the outcome of a 1, 4-dipolar cycloaddition. Four electrons are distributed among four atoms, one of which has a formal positive charge, and the other three have electron pairs. Because there is no conjugation, inter-changeability of formal charges, which is a characteristic of 1, 3- dipoles, is absent in 1, 4-dipoles. Two new σ bonds are generated one after the other following a two-step addition mechanism. The l, 4-dipole will only combine with dipolarophiles with solid electrophilic or nucleophilic reactivity. Hetero-Diels Alder reaction is one of the prominent 1, 4-dipolar cycloadditions used to make six-membered heterocycles. The production of 1, 4-dipoles from isoquinoline-DMAD and aldimine-DMAD was first reported by Huisgen (Huisgen and Herbig 1965).



Scheme 1.4 Huisgen 1, 4-dipoles

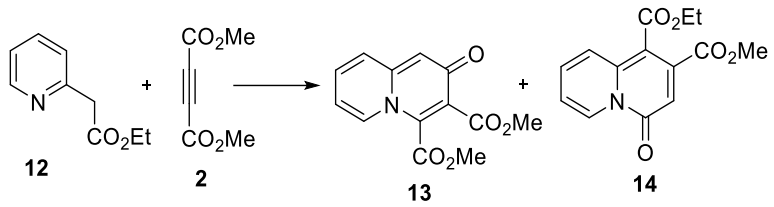
The heteroatom lone pair first adds to the π bond, followed by an electron pair shift towards the heteroatom, which is the most extensively described technique for creating 1,4-dipoles. Another strategy is to combine electron-rich alkenes with electrophilic species like ketenes, resulting in 1, 4-dipolar intermediates. Since they resulted in convergent approaches for producing polycyclic systems under favourable circumstances, synthetic routes based on formal 1, 4-dipolar cycloaddition received a lot of interest. Various reagents have been utilized as 1, 4-dipole synthons, including ortho phenyl substituted diesters, phthalide sulfones, phthalides, cyanophthalides, and *ortho*-tolyl carboxylates and vinyl isocyanates (**Scheme 1.5**) (Howe et al. 1985).



Scheme 1.5

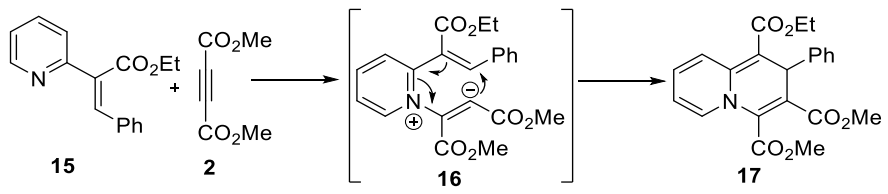
1.1.1 Pyridine, Quinoline, and Isoquinoline as 1, 4- dipole synthons

Because of the wide range of transformations that pyridines, quinolines, and isoquinolines can mediate, they demand special attention in cycloaddition reactions. The pioneering work on pyridine- DMAD zwitterion reaction dates back to 1932. Substituted pyridines also form zwitterionic intermediates, which react intramolecularly to produce ring-fused complexes. In the case of ethyl pyridyl acetate, Winterfeldt and Naumann demonstrated that intramolecular cyclization of the 1, 4-dipole to a carbonyl group is possible, resulting in the synthesis of 2H-quinolizone as the primary product (Winterfeldt 1965) (**Scheme 1.6**).



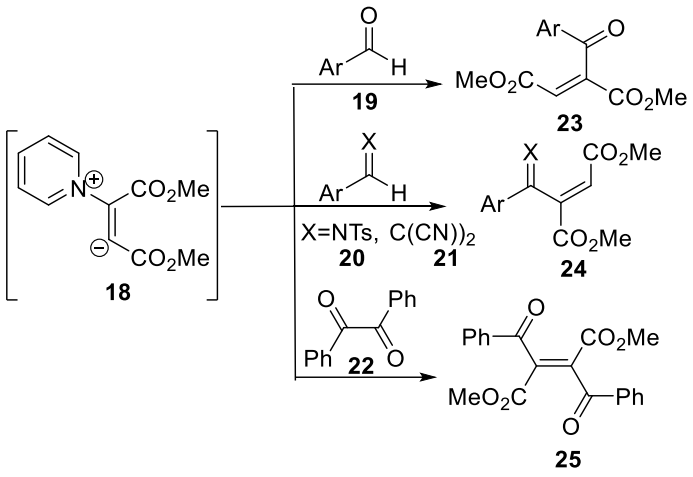
Scheme 1.6

Similarly, an intermediate formed from the reaction of ethyl-3-phenyl-2-(pyridine-2-yl) acrylate with DMAD cyclized intramolecularly to the olefinic link to yield 2H-quinolizone directly (Acheson et al. 1976) (**Scheme 1.7**).



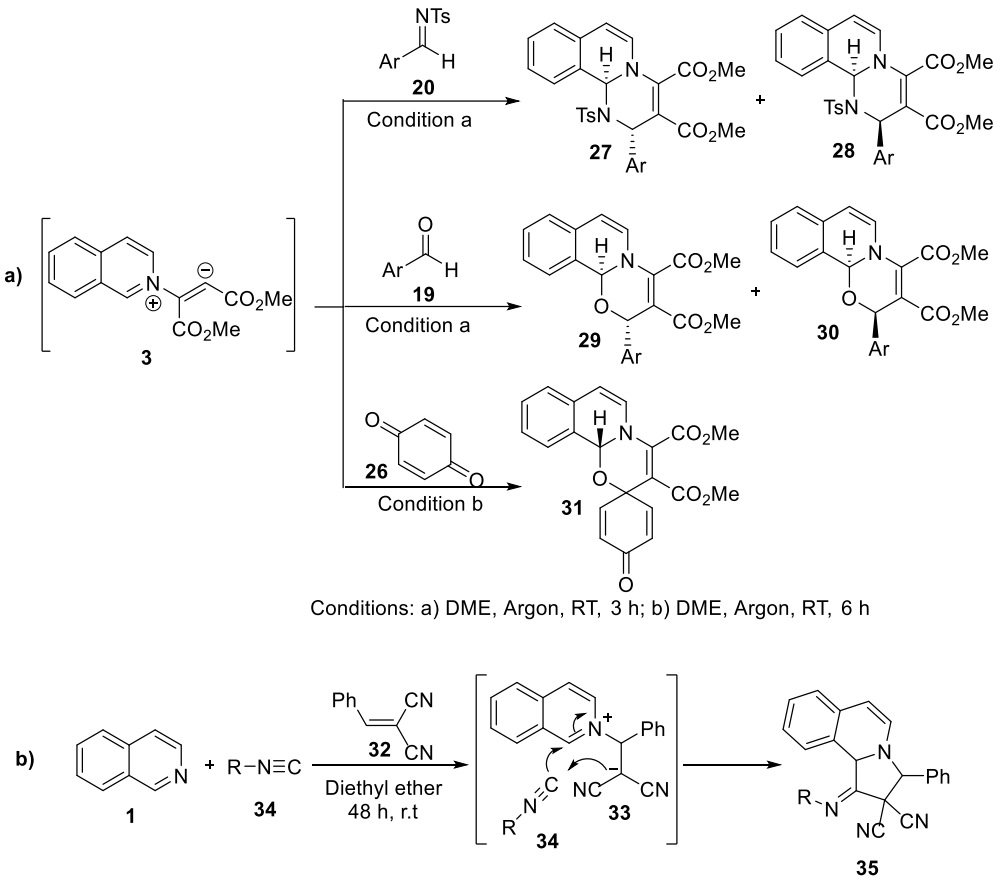
Scheme 1.7

The pyridine- DMAD zwitterion has been discovered to react with a range of carbonyl compounds, tosylimines, and activated alkenes, yielding several valuable chemicals (**Scheme 1.8**) (Nair et al. 2006, 2014; Vijay Nair et al. 2001).



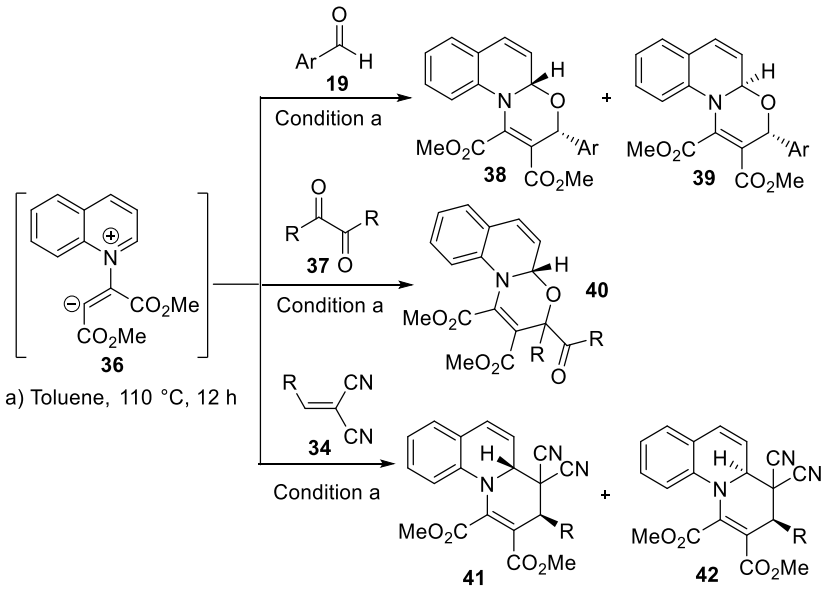
Scheme 1.8

Similarly, isoquinoline and quinoline can also produce dipoles with DMAD. These dipoles can be trapped with dipolarophiles such as dimethyl azodicarboxylate, phenyl isocyanate, diethyl mesoxalate, etc., to produce various heterocycles. The diastereoselective synthesis of 2H-pyrimido[2,1-a]isoquinoline derivatives has been demonstrated using the 1,4-dipole generated from isoquinoline and DMAD in combination with N-tosylimines (Vijay Nair et al. 2002). Spiro[1,3]oxazino[2,3-a]isoquinoline derivatives are produced in high yields by a new three-component reaction involving a 1,4-dipolar intermediate formed by adding isoquinoline to dimethyl acetylenedicarboxylate and 1,2- and 1,4-benzoquinones (Nair et al. 2003) (**Scheme 1.9 a**). A combinatorial technique was used to discover a three-component reaction involving isoquinoline, isothiocyanates, and isocyanides that produces zwitterionic imidazoisoquinolines. This reaction is a novel method to build imidazole complexes (Mironov et al. 2005) (**Scheme 1.9 b**).



Scheme 1.9

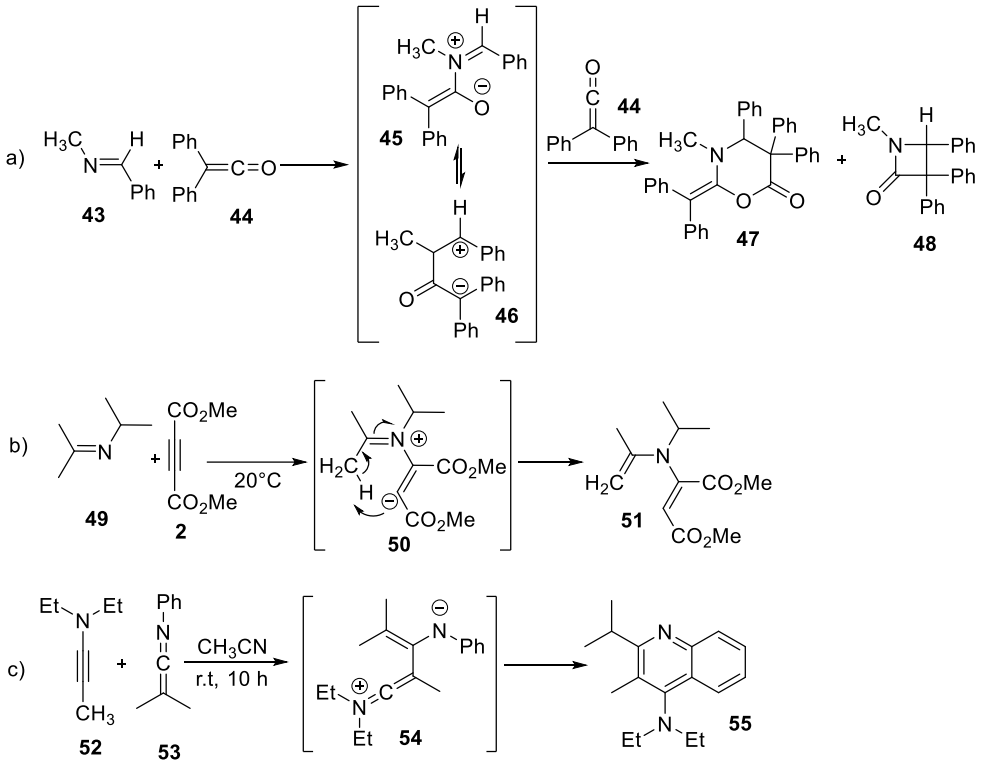
The intermediate formed by reacting quinoline with DMAD is easily added to the carbonyl group of aldehydes and 1, 2- dicarbonyl compounds. The synthesis of pyridoquinoline derivatives in good yields was achieved by three-component condensation of arylidene malononitriles and aryl cyanoacrylates with the quinoline-DMAD zwitterion (Nair et al. 2008) (**Scheme1.10**).



Scheme 1.10

1.1.2 Imine, Enamines, and Ynamines as 1, 4- dipole synthons

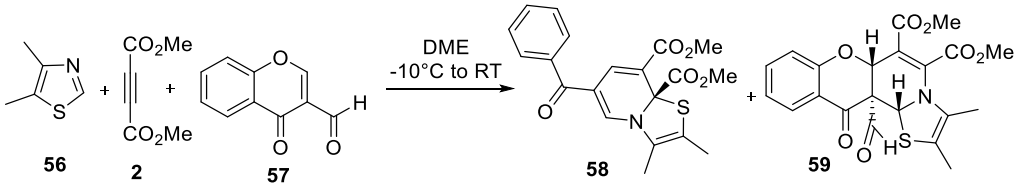
The production of 1, 4-dipoles by the direct or conjugate addition of nucleophilic N atom of imines, enamines, and ynamines to electron-deficient carbon centres has been reported. The first report in this field is the 1, 4-dipolar reactions of imines with ketenes to generate β- lactams reported by Staudinger in 1910 (**Scheme 1.11 a**). Huisgen also discovered that the 1, 4-dipole formed by benzaldimine and dimethyl acetylenedicarboxylate (DMAD) underwent 1, 4-dipolar cycloaddition with a second DMAD molecule to make the [4+2] cycloadduct. A similar reaction of ketimine with DMAD also results in a two-component product by intramolecular proton abstraction (**Scheme 1.11 b**). Ghosez et al. introduced a novel intramolecular cycloaddition of the 1,4-dipole generated from ynamine and N-phenyl ketenimine, which resulted in the one-pot synthesis of 4-aminoquinoline derivatives in high yields (Ghosez and de Perez 1971). 1, 4-dipole formed between the alkene and the enamine gets added to the second alkene molecule to produce a cyclohexane derivative (Brannock et al. 2002).



Scheme 1.11

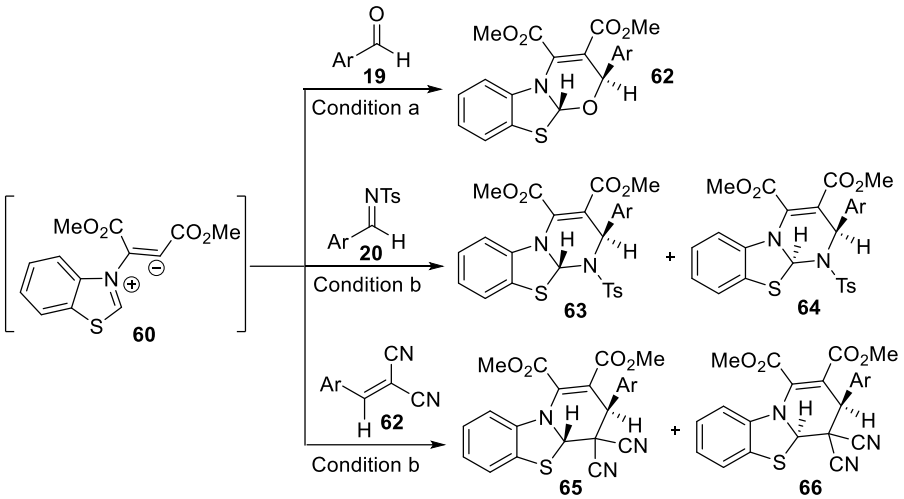
1.1.3 Benzothiazole, Thiazole and N- substituted imidazoles as 1, 4- dipole synthons

In 1964, Reid and co-workers proved the addition of thiazole to DMAD from the NMR study of the adduct formed (Reid et al. 1964). The 1, 4-dipole produced by 4,5-dimethylthiazole and DMAD has been found to react quickly with chromone-3-carboxaldehydes, leading to the simple synthesis of thiazolo[3,2-a]pyridine derivatives after an unusual rearrangement; in some instances, tetracyclic chromenothiazolopyridines were generated (Terzidis et al. 2009) (**Scheme 1.12**).



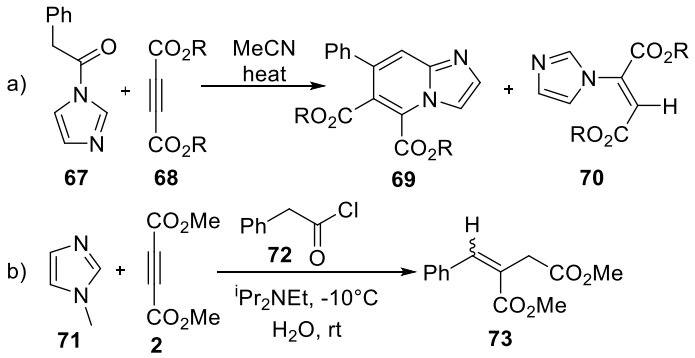
Scheme 1.12

The reaction of the zwitterion formed from benzothiazole and DMAD with activated styrenes results in a unique three-component condensation reaction that provides easy and one-pot access to the synthesis of different thiazafluorene derivatives. Preliminary investigations revealed that the benzothiazole-DMAD zwitterion combines with N-tosylimines to produce thiadiazafluorene derivatives as well (Nair et al. 2007). While the stereoselective product was obtained by reacting the benzothiazole and DMAD zwitterion with aldehydes, reactions with N-tosylimines and arylidene malononitriles produced diastereomeric mixtures (**Scheme 1.13**).



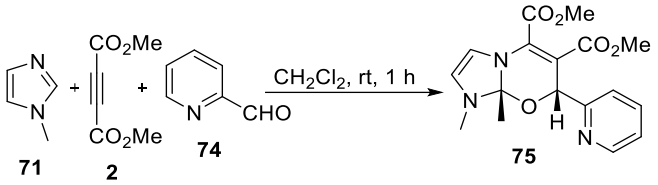
Scheme 1.13

The initial report on the reactivity of N- alkyl imidazole with DMAD was published by Bamfield and co-workers. The 1, 4-dipole from N-acylimidazole undergoes an unusual cyclization resulting imidazo[1,2-a]pyridine ring system, which was identified initially by Knölker and his group (Knölker and Boese 1988) (**Scheme1.14 a**). Dimethyl 2-arylidenesuccinates can be synthesized from a 1-methylimidazole-catalyzed reaction of DMAD with in situ generated arylketenes (Hanfeng Ding et al. 2005) (**Scheme1.14 b**).



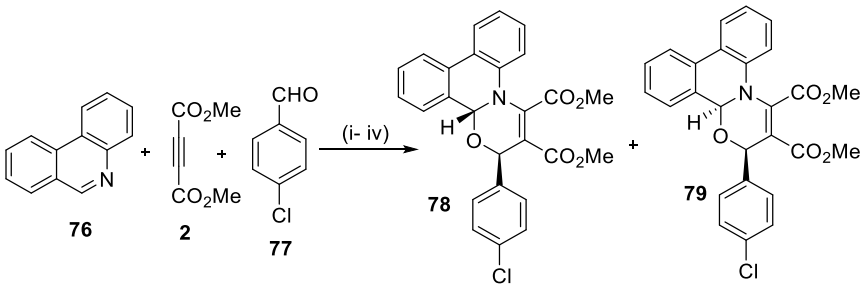
Scheme 1.14

In the presence of pyridine carboxaldehydes, 1-alkyl imidazoles react smoothly with dialkyl acetylenedicarboxylates to form 1,8 a -dihydro-7*H*-imidazo[2,1-b][1,3]oxazine derivatives. The 1,4-dipole reacts with the aldehyde to make the oxyanion intermediate, which then undergoes ring closure to produce the three-component product (Adib et al. 2006) (**Scheme 1.15**).



Scheme 1.15

A three-component reaction involving phenanthridine, dimethyl acetylenedicarboxylate (DMAD), and aromatic aldehydes is disclosed for the efficient synthesis of [1, 3] oxazino[3,2-f]phenanthridine derivatives. This innovative approach follows the Huisgen 1,4-dipolar cycloaddition reaction of phenanthridine – DMAD dipole (Li et al. 2011).

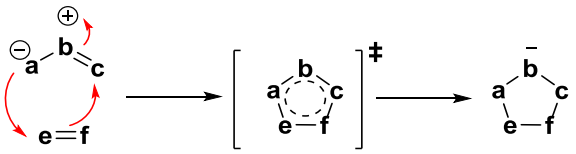


i) $^{i}PrNEt_2$, -10°C; ii) H_2O, RT; iii) CH_2Cl_2, 1 h, iv) CH_2Cl_2. RT, 24 h

Scheme 1.16

1.2. 1, 3- DIPOLAR CYCLOADDITION REACTIONS

Smith first proposed the concept of 1, 3-dipolar cycloadditions in 1938 (Smith 1938), and Rolf Huisgen detailed this in numerous lectures during the 1960s. Because of the high degree of regio- and stereo control that comes with the 1, 3-dipolar cycloaddition, which is thermally permitted by the Woodward–Hoffmann rules (Hoffmann and Woodward 2002), it is a versatile synthetic technique in organic synthesis, especially in the synthesis of heterocycles and natural products (Padwa and Pearson 2003). Over the last 50 years, there has been a tremendous amount of research in the field of 1,3 - dipolar cycloadditions, and the reaction is currently used in practically every area of chemistry, from materials chemistry (Jun Zhu et al. 2008; Lee et al. 2009) to drug discovery (Antoni Krasiński et al. 2005; Tron et al. 2008), demonstrating its versatility.

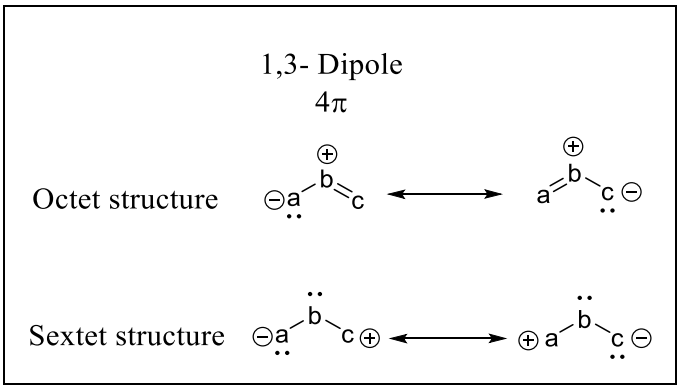


Scheme 1.17

1.2.1 The 1, 3- dipoles/ ylides and dipolarophiles

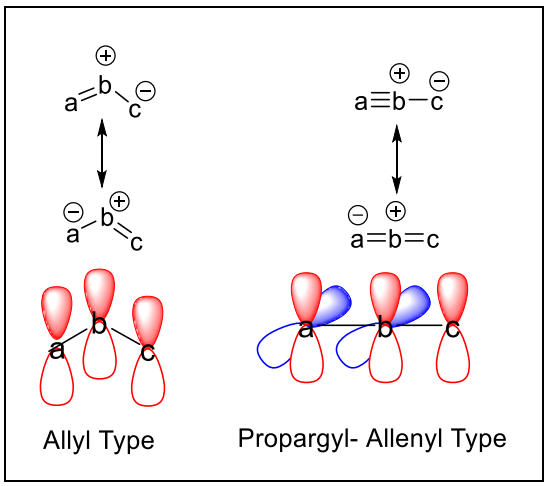
The 1, 3-dipole, also known as ylide, is a three-atom π-electron system with four π-electrons distributed over the three atoms. As demonstrated, a 1, 3-dipolar molecule is represented by zwitterionic octet and sextet structures (**Scheme 1.18**). The three atoms can be any combination of carbon, oxygen, and nitrogen. There are four electrons in

three parallel π-orbitals in all 1, 3-dipoles, and they are both nucleophilic and electrophilic. Comparatively, the nucleophilic property may be more potent than its electrophilic property. Compounds like nitrile ylides and diazomethane add to electron-deficient dipolarophiles much faster than the compounds with electron-rich multiple bonds. The sextet formulations have little effect on the resonance hybrid's electron distribution. Still, they show the ambivalence of the 1, 3-dipole, which is essential for understanding the mechanism, reactivity, and regiochemistry of 1, 3-dipolar cycloadditions.



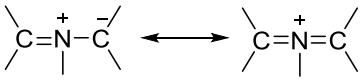
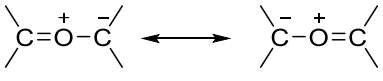
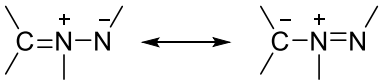
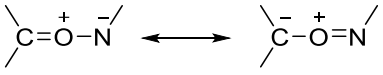
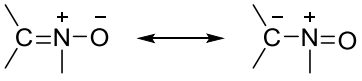
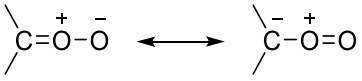
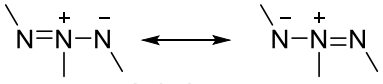
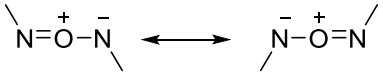
Scheme 1.18

The allyl anion type and the propargyl–allenyl anion type are the two varieties of 1, 3-dipoles. Four electrons in three parallel p_z orbitals perpendicular to the dipole plane characterize the allyl anion type. The presence of a double bond orthogonal to the delocalized π-system in the propargyl–allenyl anion type confers linearity to the dipoles of the propargyl–allenyl anion type (**Scheme1.19**).



Scheme 1.19

The core atom b in allyl type dipoles can be a group V (e.g., N or P) or a group VI element (e.g., O or S). Because only atoms from this group can have a positive charge in the quartervalent state, 'b''s role is limited to propargyl–allenyl types. Six propargyl–allenyl dipoles and twelve allyl dipoles can be generated by confining 'a' and 'c' to second-row elements (C, N, O) (**Table 1.1 and Table 1.2**) (Huisgen 1963).

A) Allyl type 1, 3- dipoles	
 Azomethine ylides	 Carbonyl ylides
 Azomethine Imines	 Carbonyl imines
 Nitrones	 Carbonyloxides
 Azimines	 Nitrosimines

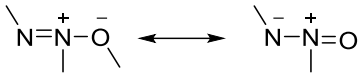
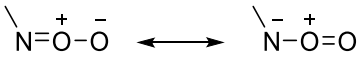
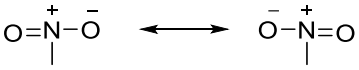
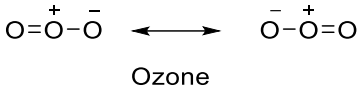
 Azoxy compounds	 Nitrosoxides
 Nitro compounds	 Ozone

Table 1.1 Allyl type 1, 3- dipoles

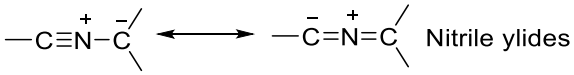
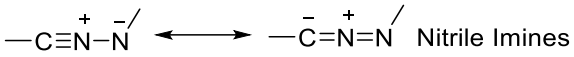
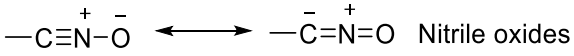
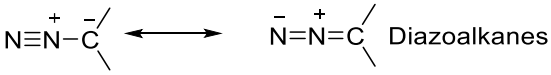
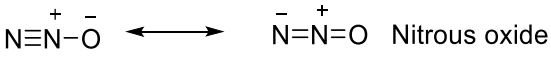
B) Propargyl- Allenyl type 1, 3- dipoles
 Nitrile ylides
 Nitrile Imines
 Nitrile oxides
 Azides
 Diazoalkanes
 Nitrous oxide

Table 1.2 Propargyl- Allenyl type 1, 3- dipoles

The dipolarophile is the 2π component of the 1, 3-dipolar cycloaddition. Almost any double or triple bond can be used as a dipolarophile. The π bond systems such as, **C≡C**, **C≡N**, **C=O**, **C=N** etc. can act as dipolarophile. The most prevalent dipolarophile

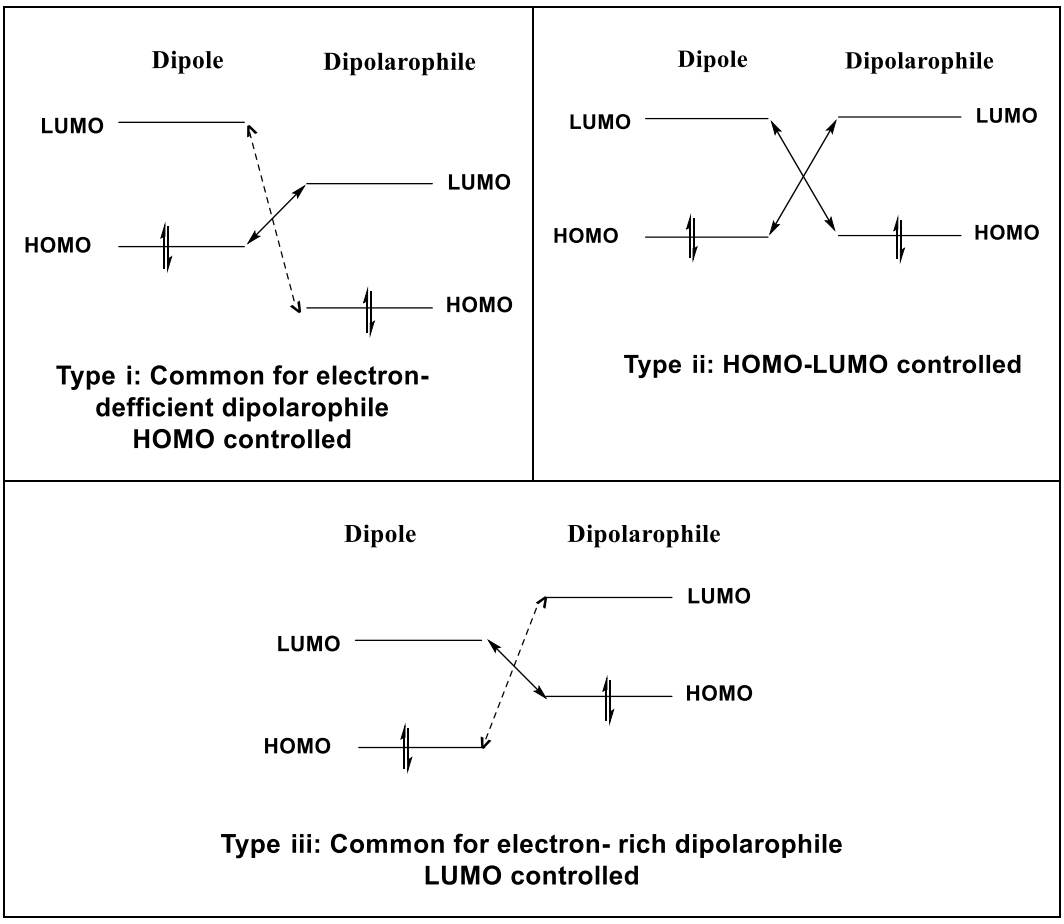
compounds are alkynes, carbonyls, and nitriles. Imines, azo, nitroso, etc. serve as examples of multiple bonded functional groups operating as dipolarophiles. Electron withdrawing or electron-donating functionalities can enhance the reactivity of dipolarophiles. But the presence of both the functionalities at a time decreases the dipolarophilic nature of the molecule. Because of the structural diversity of dipolarophiles, 1, 3-dipolar cycloadditions are extremely useful and adaptable in heterocyclic synthesis.

1.2.2 Mechanistic aspects of 1, 3- dipolar cycloaddition

Huisgen hypothesized that a concerted, pericyclic shift occurs between the dipolarophile's 2 π-electrons and the dipolar compound's four electrons. The reaction is a [2s+4s] cycloaddition and is analogous to the Diels-Alder reaction since the addition is stereo-conservative (suprafacial). The purely cis-nature of the additions, in which the geometrical relationships among the substituents on both the reactants are preserved in the product, is the best evidence supporting Huisgen's concerted mechanism. A specific resemblance of the interacting HOMO and LUMO orbitals, depending on the respective orbital energies of both the dipolarophile and the dipole, is a requirement for such a reaction to occur. Electron-withdrawing groups on the dipolarophile usually favour an interaction of the dipolarophile's LUMO with the dipole's HOMO, resulting in new bonds. In contrast, electron-donating groups on the dipolarophile usually favour the inverse of this interaction, resulting in the formation of new bonds. Frontier orbital theory can explain the regioselectivity of 1, 3-dipolar cycloadditions since the frontier orbital coefficients regulate the transition state.

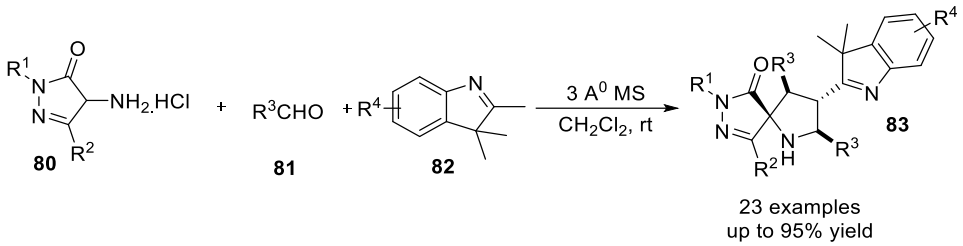
Sustmann divided 1, 3-dipolar cycloadditions into three groups, Types I–III, based on the character of the substituents on the dipole and dipolarophile (Sustmann 1971).

i) Interaction between LUMO of the dipolarophile and HOMO of the dipole.
ii) The dipole and dipolarophile's frontier orbital energies are pretty similar, and a combination of any HOMO-LUMO interaction can occur.
iii) Interaction between HOMO of the dipolarophile and LUMO of the dipole.



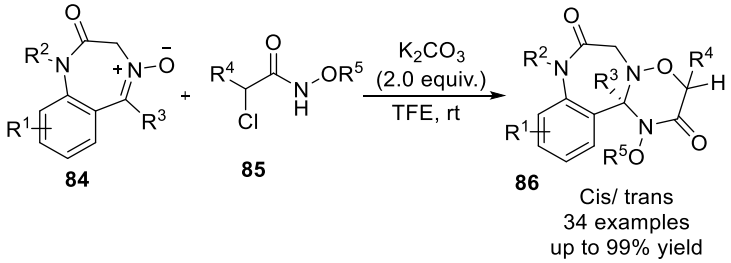
Scheme 1.20

1, 3-dipolar cycloadditions are likewise highly stereoselective, with the initial dipolarophile's stereochemistry preserved in the final product. Several reports on the synthesis of various heterocycles based on 1, 3- dipolar cycloadditions have been proposed to date. A one-pot [3 + 2] cycloaddition of 4-aminopyrazolones, indolenines, and aldehydes was reported very recently by Shah Nawaz and co-workers. Under simple conditions, the reaction in situ generated azomethine ylides as 1, 3-dipoles, and 2-alkenylindolenines as dipolarophiles, yielding indolenine-derived spiro[pyrazolone-4,2′-pyrrolidine] scaffolds (Nawaz et al. 2021).



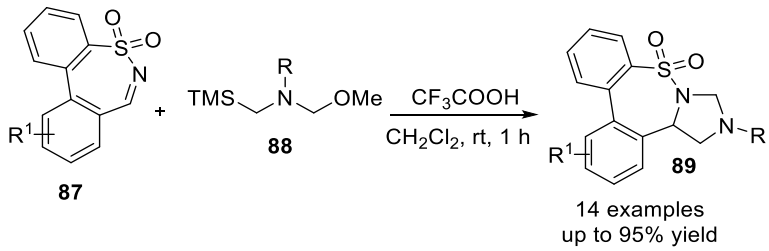
Scheme 1.21

The 1,3-dipolar [3+3] cycloaddition between 1, 4-benzodiazepinone-based nitrones and α-halohydroxamates, which was promoted by K_2CO_3 (2.0 equiv), proceeded smoothly under mild reaction conditions, yielding structurally novel and complex cis- or trans-configured d-edge heterocycle-fused 1,4-benzodiazepinones (Zhang et al. 2021).



Scheme 1.22

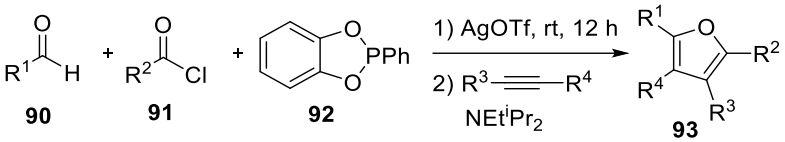
Kai- Kai Wang et al. reported the synthesis of functionalized polycyclic sulfonamides containing ε-sultams via a [3+2] 1, 3- dipolar cycloaddition reaction (Wang et al. 2021).



Scheme 1.23

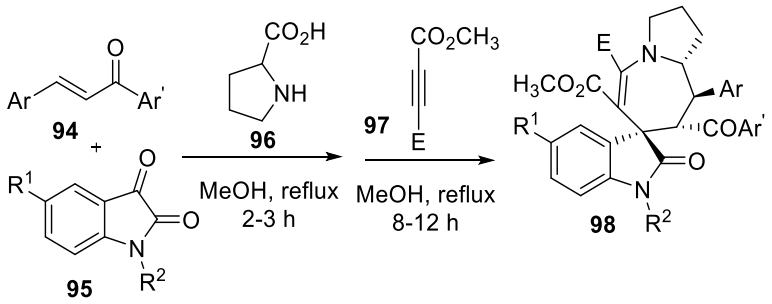
Huseyin Erguven and the research group proved that the multi-component reaction of aldehydes, acid chlorides, and the phosphonite PhP(catechyl) can produce a new class of phosphorus-containing 1, 3-dipoles. Combining the dipole generation with 1,3-

dipolar cycloaddition provides a unique, modular route to furans from a variety of aldehydes, acid chlorides, and alkynes, with independent control of all four substituents (Huseyin Erguven et al. 2021).



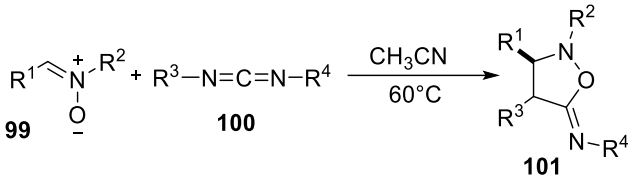
Scheme 1.24

A one-pot two-step reaction yielding novel ferrocenyl and styryl-substituted spiro compounds using chalcones, ferrocenyl-chalcones, and dibenzylideneacetones were described by Wen- Tao Wu et al. The domino [3+2] cycloaddition reaction of azomethine ylide with chalcone and the ring-expansion reaction of in situ generated spiro[indoline-3,3′-pyrrolizine] with electron-deficient alkynes are the critical steps involved in the reaction (Wu et al. 2020).



Scheme 1.25

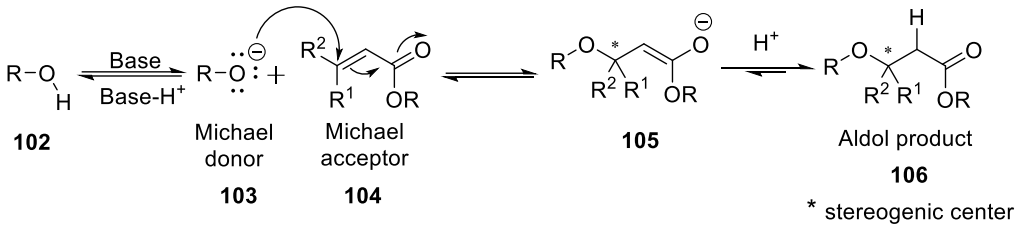
Yuan Chen and co-workers have developed a [3+2] cycloaddition of nitrones and carbodiimides with high efficiency. High regioselectivity, mild and metal-free conditions, excellent functional group compatibility, and a broad substrate scope characterize this 1,3-dipolar cycloaddition. X-ray structures of two regio-isomers confirmed the regioselectivity of this transformation (Chen et al. 2019).



Scheme 1.26

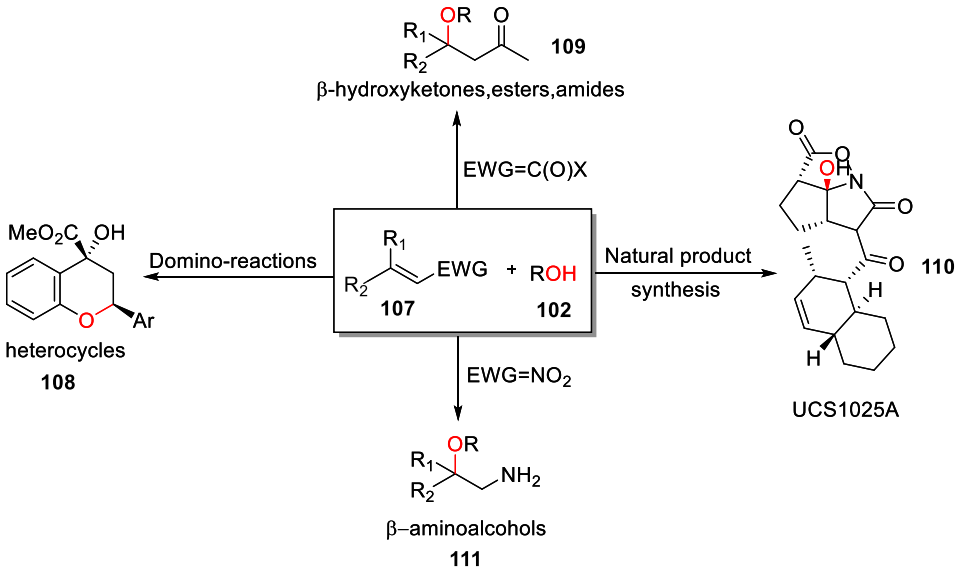
1.3 MICHAEL ADDITION AND OXA- MICHAEL ADDITION REACTIONS

Michael addition reaction followed by cyclization is a facile technique for heterocycle synthesis. The carbon-carbon bond formation in organic synthesis by adding carbon nucleophiles to conjugate acceptor systems is known as Michael addition reactions (Vicario et al. 2007). Hetero-Michael addition (Reiter et al. 2006; Wabnitz et al. 2004; Wipf and Graham 2005), which involves the addition of non-carbon nucleophiles such as amines (Enders et al. 2009), thiols (Jackson et al. 2016; Sharma and Degani 2007), phosphorus, and alcohols to Michael acceptors has become increasingly important in recent decades. In contrast to Michael reactions, oxa-Michael reactions have lately been adopted as standard transformations in chemical synthesis because the potential products of these strategies are valuable intermediates. The oxa-Michael reactions are the most effective and efficient approach to make numerous oxygen-containing heterocycles with five and six members, such as tetrahydropyrans, tetrahydrofurans, 1,4 dioxanes, isoxazolines, lactones, and related butenolides(Ahmad and Ullah 2021a). The relevance of oxa-Michael reactions is highlighted because these molecular frameworks led to the synthesis of numerous biologically active medications with high complexity in a single step. Loydl reported the first oxa-Michael reaction in 1898, which was the conjugate addition of an alcohol to a Michael acceptor to produce maleic acid. In general, carboxylic acids, alcohols, phenols, oximes, and hydrogen peroxides are used as hydroxyl pronucleophiles, while Michael acceptors include α,β-unsaturated esters, α,β-unsaturated acids, nitroolefins, α,β-unsaturated nitriles, α,β-unsaturated sulfones, and others.



Scheme 1.27

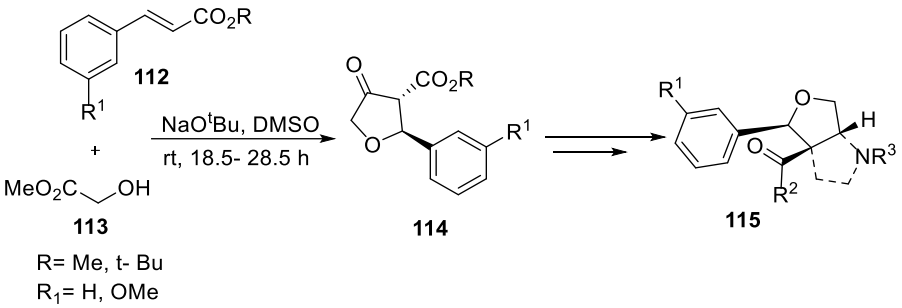
The reversibility of the alcohol addition and the comparatively weak nucleophilicity of the alcohols are often significant limitations of oxa-Michael reactions. This makes intermolecular oxa-Michael reactions particularly difficult. However, oxa-Michael reactions frequently provide fast access to oxygen-containing heterocycles, including tetrahydropyrans, chromenes, and xanthones, frequently found in natural products (Tang et al. 2006). Hence its application is extended towards the total synthesis of Brevetoxin B (Nicolaou et al. 2002), Aculeatin A (Yao et al. 2014), Azaspiracid (Geisler et al. 2004), Cortistanin A (Nicolaou et al. 2008), (+)- conical (Hong et al. 2010) and so on.



Scheme 1.28: Synthetic applications of Oxa-Michael reaction (F. Nising and Stefan Bräse 2008)

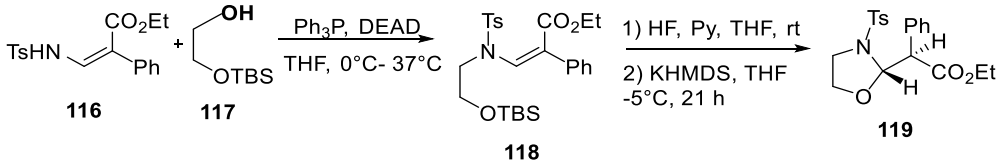
The strategy is widely used to synthesize five and six-membered oxygen heterocycle constructions (Ahmad and Ullah 2021). THFs and pyrrolidino-THFs with 2-aryl, 3-

carboxy, and 4-amino functionalities have been produced by Dr. Steven M. Wales et al. The precursor 4- oxofurans were readily synthesized via oxa-Michael/ Dieckmann annulation reactions. Diastereoselective reductive amination of the pre- functionalized precursor results in the THF cores (Wales et al. 2018).



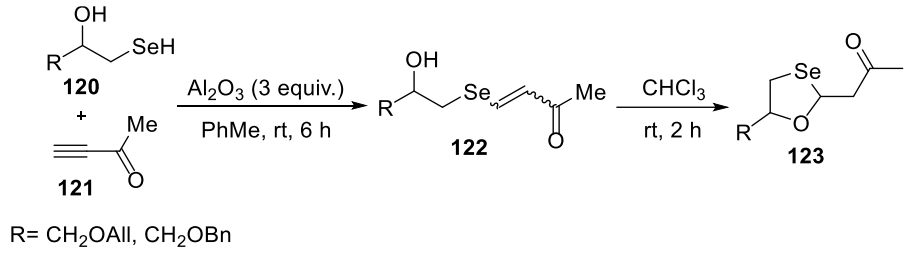
Scheme 1.29

Synthesis of oxazolidines processing two contiguous stereocenters in a single step was described by Chakraborty et al. The reaction route employed α-phenyl-β-enamino ester as a nucleophilic synthon for Mitsunobu alkylation, to avoid the reversibility of the addition step (Khan and Chakraborty 2018).



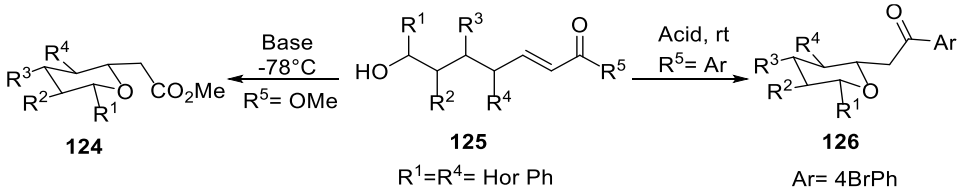
Scheme 1.30

In 2019, Tanini et al. reported the addition of stable functionalized primary alkyl selenols to activated alkenes and alkynes through the Seleno-Michael method. The intermediate formed in the seleno-Michael reaction between 1,2-hydroselenoalcohol and activated alkynes undergoes intramolecular cyclization to yield the final product (Tanini et al. 2019).



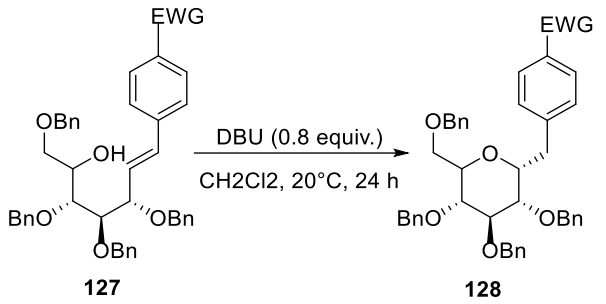
Scheme 1.31

Intramolecular oxa- Michael addition for the synthesis of 2,3-, 2,4- and 2,6- substituted tetrahydropyrans (THP) were reported by Dániel Csókás and co-workers (Csókás et al. 2019). Both acidic catalysis and basic catalysis were employed to study the effects of the reaction. In both cases, the reaction was kinetically controlled. Acidic catalysis yielded the di-equatorial product exclusively, whereas the axial-equatorial isomer is generally favoured under basic conditions.



Scheme 1.32

A novel benzyl C-glycoside preparation involving the intramolecular oxa-Michael cyclization of styryl compounds has been established. The precursor substrate was prepared via the cross-metathesis of electron-poor styrene and olefins. Only reactive substrates with strong electron-withdrawing groups were used in the conjugate addition (NO_2, SO_2Ph). The less reactive styryl derivatives (CHO, COMe, CO_2Me) with weak electron-withdrawing groups were unreactive and failed to provide the expected result (Redon et al. 2013).



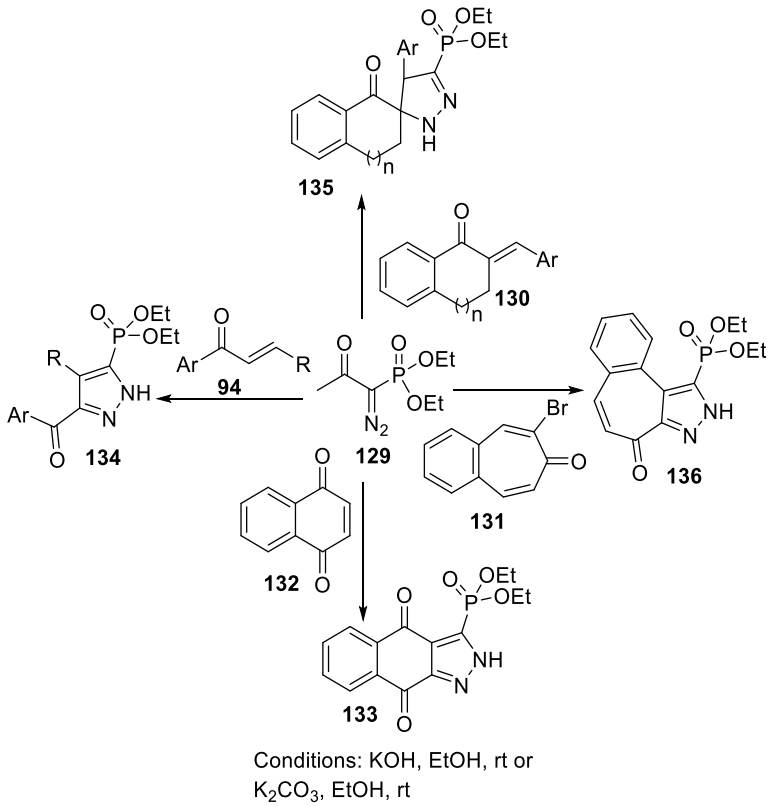
127 128

Scheme 1.33

1.4 LITERATURE REVIEW

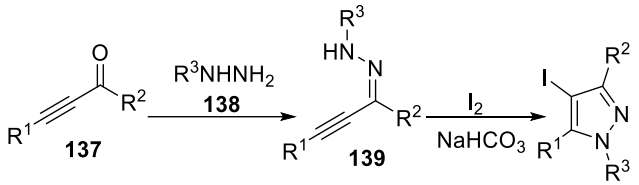
Part A: This section covers a brief literature review on the various synthetic methods towards pyrazoles and substituted pyrazoles.

Deepti Verma and co-workers have synthesized single regioisomers of novel carbonylated pyrazole phosphonates by treating conjugated enones, dienones, tropones, and quinones with the Bestmann- Ohira reagent at room temperature under KOH/EtOH conditions. Under K_2CO_3/EtOH conditions, a similar reaction involving R-arylidenecycloalkanones generated spiropyrazoline phosphonates as single regio- and diastereomers in high yield (Verma et al. 2011).



Scheme 1.34

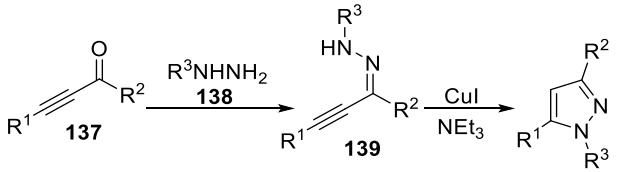
Metin Zora in 2011 studied the synthesis of 4-iodopyrazoles, via electrophilic cyclizations of α, β-alkynic hydrazones by molecular iodine. Hydrazines were quickly made into α, β-alkynic hydrazones by reacting with propargyl aldehydes and ketones. α, β -alkynic hydrazones underwent electrophilic cyclization in the presence of sodium bicarbonate when treated with molecular iodine, yielding 4-iodopyrazoles in good to high yields. Iodocyclization was found to be universal for a wide range of α, β - alkynic hydrazones, tolerating aliphatic, aromatic, heteroaromatic, and ferrocenyl moieties with electron-withdrawing and electron-donating substituents (Zora and Kivrak 2011).



R^1= Alkyl, Aryl, Ferrocenyl
R^2= H, Methyl, Phenyl
R^3= Alkyl, Aryl

Scheme 1.35

The same group in 2011, reported the electrophilic cyclization of α, β-alkynic hydrazones by copper (I) iodide to generate pyrazoles. The starting material undergoes electrophilic cyclization to give pyrazole derivatives in good to exceptional yields when treated with copper (I) iodide in the presence of triethylamine in refluxing acetonitrile(Zora et al. 2011).

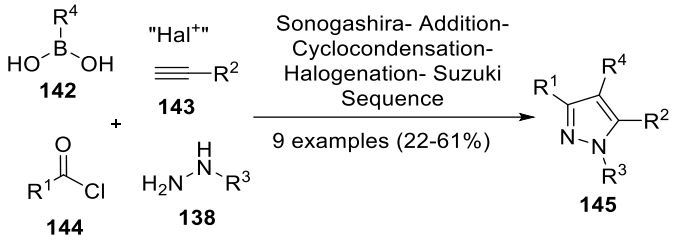


R^1= Alkyl, Aryl, Ferrocenyl
R^2= H, Methyl, Phenyl
R^3= Alkyl, Aryl

Scheme 1.36

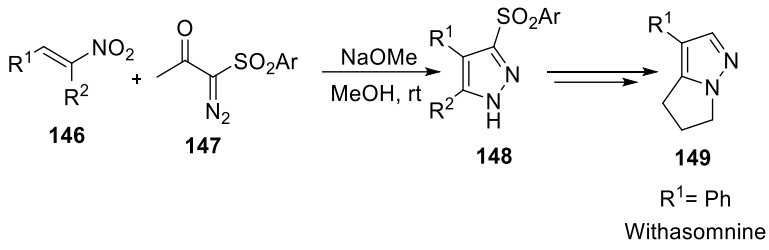
In a one-pot four-step procedure that includes - Sonogashira coupling, addition-cyclo condensation, bromination, and Suzuki coupling in sequence – highly functionalized 1,3,4,5-tetrasubstituted pyrazoles were synthesized quickly and effectively by Benjamin Willy and Thomas J. J. Muller in 2011. The electron-rich, electron-poor, (hetero) aromatic starting materials, aliphatic substituents are well tolerated, which

concludes the scope of this methodology is quite extensive. The second and last steps in the reaction are microwave-assisted, and the terminal step requires no additional Pd catalyst, according to sequential catalysis. In solution, per substituted pyrazoles synthesized exhibit a bright blue fluorescence with substantial Stokes shifts (Willy and Müller 2011).



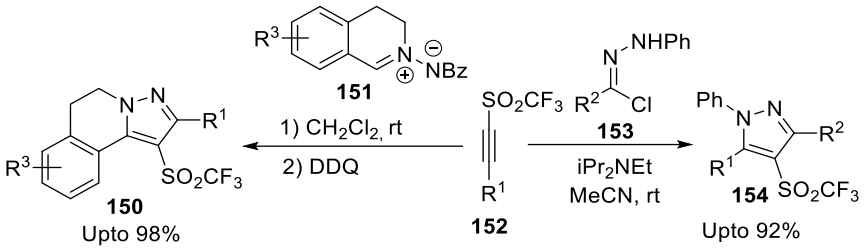
Scheme 1.37

In a one-pot room temperature process, a base-mediated reaction of α-diazo-β-ketosulfone with nitroalkenes yields sulfonylpyrazoles as single regioisomers in outstanding yield. Rahul Kumar and Irishi N. N. Namboothiri reported this specific synthesis of pyrazole derivative in 2011. Using the right nitroalkenes, the group successfully inserted aryl, heteroaryl, styrenyl, alkyl, hydroxymethyl, and hydrazinyl groups into the pyrazole ring. Further, the approach was used to synthesis a pyrazole alkaloid, Withasomnine. Withasomnine has strong biological characteristics, so the prospect of finding a broad and efficient route to its complete synthesis using their methodology seemed appealing (Kumar and Namboothiri 2011).



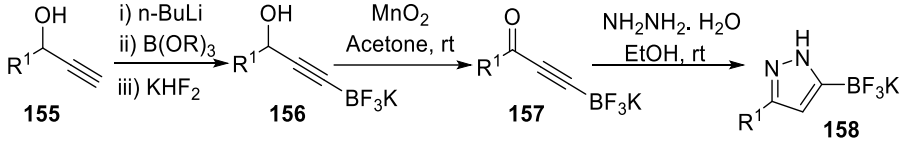
Scheme 1.38

Hiroyuki Kawai et al. in 2012 reported the regioselective synthesis of pyrazole triflones based on triflyl alkyne cycloadditions. The 1,3-dipolar cycloaddition of triflyl alkynes and hydrazonoyl chloride proceeded in the presence of Hunig's base. Biologically attractive pyrazolo[5,1-a]isoquinoline triflones were regioselectively synthesized by tandem 1,3-dipolar cycloaddition/oxidative aromatization for the first time from triflyl alkynes and C, N-cyclic azomethine imines (Kawai et al. 2012).



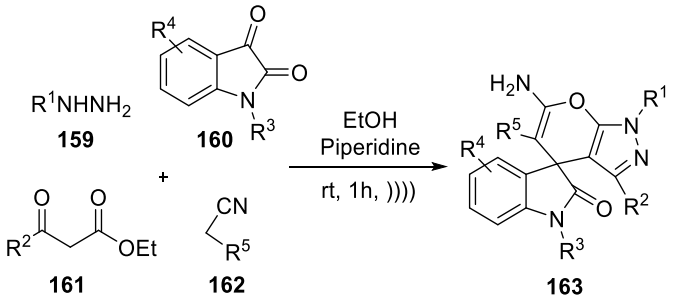
Scheme 1.39

In a two-pot procedure, pyrazole trifluoroborates were synthesized from propargylic alcohols by James D. Kirkham and co-workers. Cyclization of hydrazines to these ynone trifluoroborates was utilized to create a variety of pyrazole trifluoroborate salts. The resultant compounds were then subjected to C-C and C-N bond formation processes, yielding a variety of functionalized pyrazole scaffolds (Kirkham et al. 2012).



Scheme 1.40

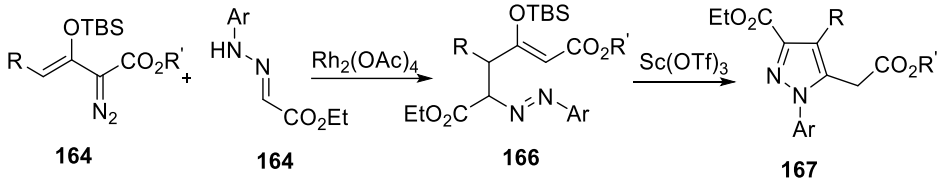
The four-component reaction of hydrazine, β-keto ester, isatin, and malononitrile/ethyl cyanoacetate, catalyzed by piperidine under ultrasonic irradiation, was described as a practical one-pot synthesis of spiro[indoline-3,4′-pyrano[2,3- c]pyrazole] derivatives by Yi Zou et al. in 2012. The product formed was separated by a simple filtration technique and characterized (Zou et al. 2012).



Scheme 1.41

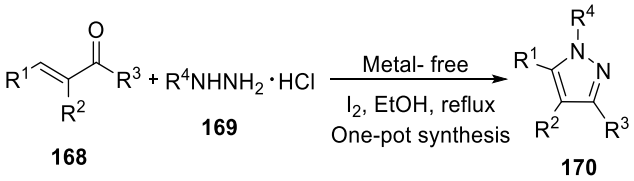
A cascade procedure started by Rh (II)-catalyzed dinitrogen extrusion from enol diazoacetates with vinylogous nucleophilic addition, followed by Lewis acid-catalyzed cyclization and aromatization has been established to produce regiospecific multifunctional pyrazoles by Xinfang Xu et al. in 2013. This reaction specifically

documents the vinylogous reactivity using the hydrazone's carbon rather than nitrogen (Xu et al. 2013).



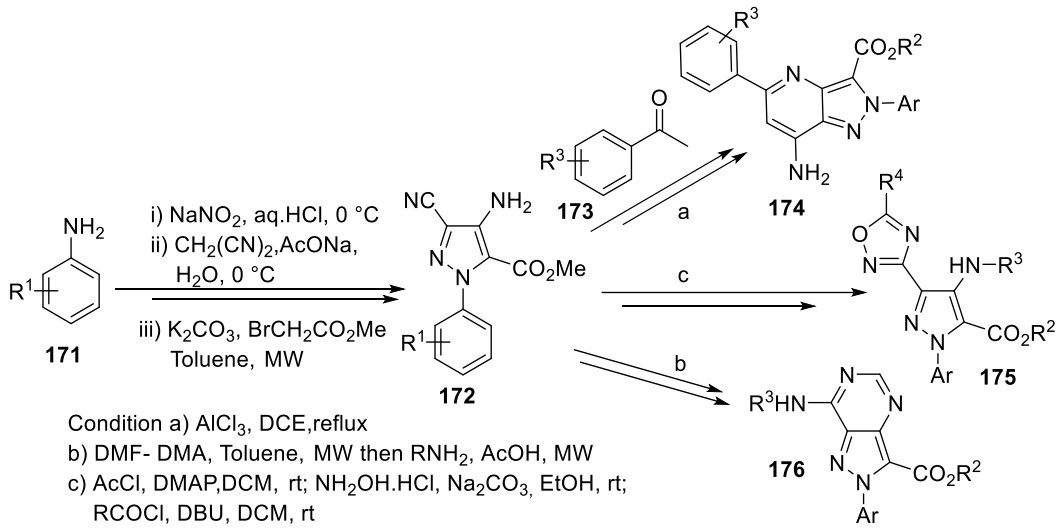
Scheme 1.42

In 2014, Xinting Zhang and co-workers proposed a metal-free oxidative C-N bond-forming technique mediated by I_2 to form regioselective pyrazole derivatives. This practical and environmentally friendly one-pot protocol eliminates the need to isolate the less stable intermediates hydrazones and provides easy access to a variety of di-, tri-, and tetra- substituted (aryl, alkyl, and vinyl) pyrazoles from readily available, α, β-unsaturated aldehydes/ketones and hydrazine salts. The reaction starts with oxidative iodination of hydrazones, followed by an S_N2-type cyclization resulting in a C-N bond. The pyrazole framework is obtained through deprotonation in the final stage (Zhang et al. 2014).



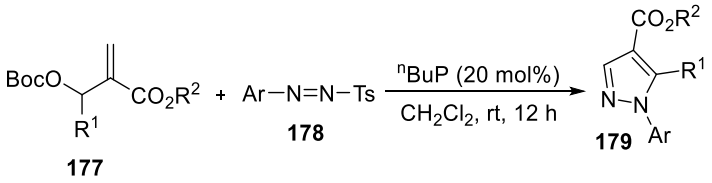
Scheme 1.43

Microwave activation was used to achieve 4-amino-3-cyano-N-arylpyrazoles based on a Thorpe–Ziegler cyclization by Laurent Le Corre and co-workers. These highly functionalized building blocks gave numerous heteroaromatic scaffolds such as pyrazolo-pyridines, pyrazolo-pyrimidines, and pyrazolo-oxadiazoles via a new diversity-oriented synthesis method. These platforms have three to four reactive sites that could be employed for post-functionalization to expand molecular diversity even further (Corre et al. 2014).



Scheme 1.44

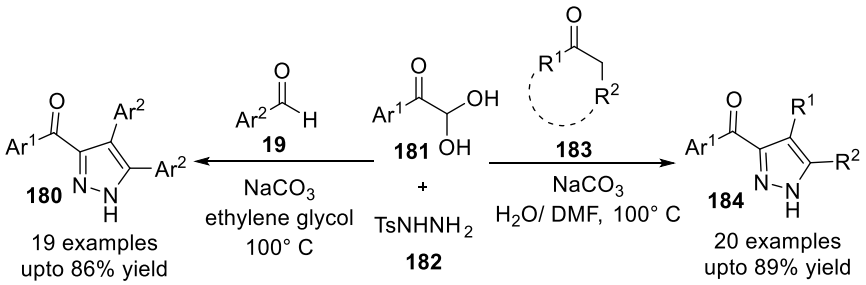
To synthesize pyrazole derivatives, $^{n}Bu_3P$-catalyzed desulfonylative [3+2] cycloadditions of allylic carbonates with arylazosulfones were established by Qi Zhang et al. Irrespective of the electronic nature of the substituents present, both arylazosulfones and allylic carbonates gave the product in moderately good yields. The reaction proceeds by adding $^{n}Bu_3P$ to allylic carbonate, followed by the formation of an allylic phosphorus ylide intermediate via an elimination deprotonation step that simultaneously eliminates carbon dioxide and t-BuOH. The intermediate formed by the γ- addition of the ylide to the arylazosulfones eliminates $^{n}Bu_3P$ leads to the formation of dihydropyrazole, further desulfonylation leads to pyrazole product (Zhang et al. 2015).



Scheme 1.45

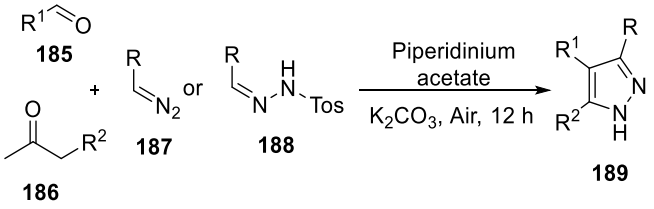
From readily available arylglyoxal monohydrates, tosylhydrazine, and ketones or aldehydes, a multi-component procedure for synthesizing polyfunctional pyrazole derivatives was established by Wen-Ming Shu et al. in 2015. The electronic structure of the substituents on the aromatic ring system of arylglyoxal monohydrates had a substantial impact on the efficiency of this transformation. Regardless of electrical characteristics, the reaction proceeded smoothly for various ketones, and the

appropriate products were produced in good to outstanding yields. The key advantages are the broad substrate scope, good regioselectivity, and ease of operation of this synthesis technique (Shu et al. 2015).



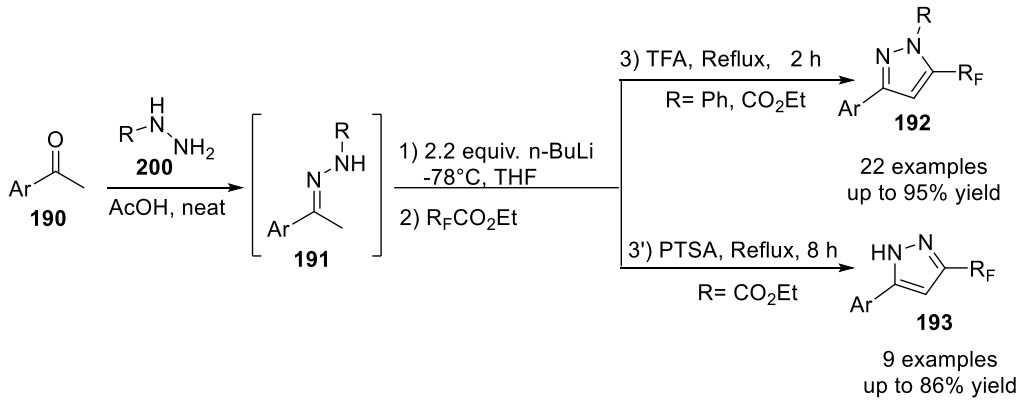
Scheme 1.46

An easy-to-implement and high-yielding methodology for one-pot, three-component coupling for synthesizing polyfunctional pyrazoles have been created by Ahmed Kamal et al. Aldehydes, 1,3-dicarbonyls, and diazo-compounds, as well as tosyl hydrazones, were used as the starting materials. The procedure uses molecular oxygen as a green oxidant and follows a tandem Knoevenagel condensation, 1,3-dipolar cycloaddition, and transition metal-free oxidative aromatization reaction sequence. By altering the aldehyde, 1,3-dicarbonyl, and diazo-components individually, the extent of the reaction was investigated (Kamal et al. 2015).



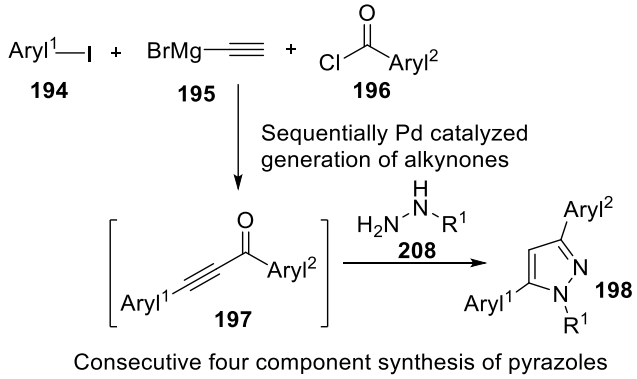
Scheme 1.47

The cyclization of hydrazine dianions with ethyl perfluorocarboxylates has been used to produce a highly selective and efficient approach for the synthesis of 5-trifluoromethylated and 5-perfluoroalkylated pyrazoles. The pyrazoles were tested for their ability to inhibit alkaline phosphatases, h-TNAP (human tissue non-specific alkaline phosphatase), and IAP (tissue-specific intestinal alkaline phosphatase). According to the results, the majority of the compounds reported suppressed h-IAP more effectively than h-TNAP. As a result, these chemicals appear to be h-IAP selective inhibitors (Ngo et al. 2015).



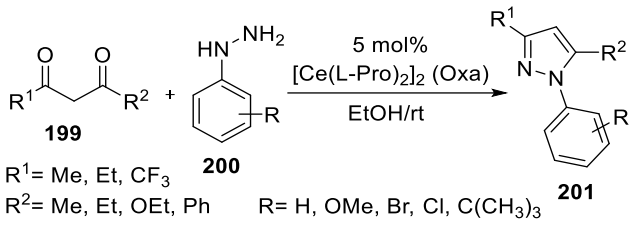
Scheme 1.48

Using the Pd-catalyzed one-pot production of alkynones from aryl iodides, ethynyl magnesium bromide, and acid chlorides, a four-component synthesis of pyrazoles and pyrimidines was reported by Alissa C. Götzinger et al. in 2016. This one-pot approach provides the rapid and diverse production of fluorophores, including donor, acceptor, and donor-acceptor substituted pyrazoles. When photonic excitation occurs, a significant charge-transfer character emerges, explaining the development of large Stokes shifts and solvatochromic behaviour of the synthesized compounds (Götzinger et al. 2016).



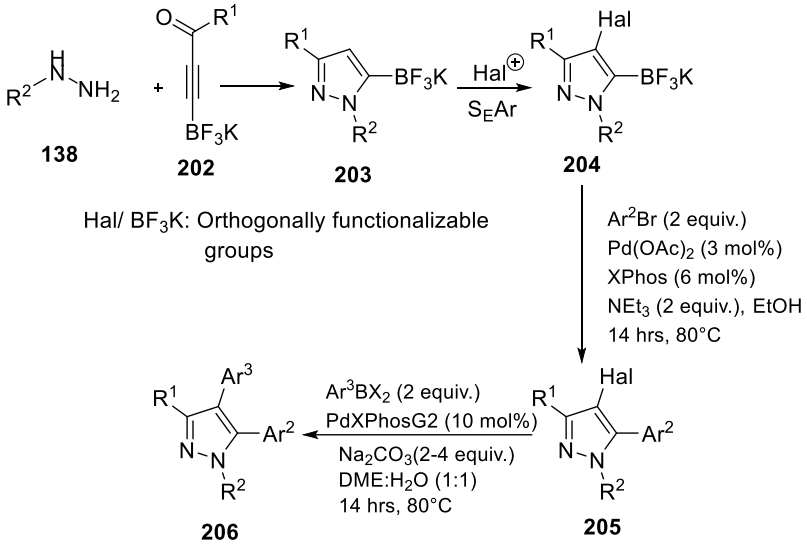
Scheme 1.49

Using 1, 3-dicarbonyl compounds and phenyl hydrazines in one pot, Ramesh Katla et al. established a unique and highly efficient protocol for synthesizing pyrazole derivatives. They employed $[Ce(L\text{-}Pro)_2]_2$ (Oxa) as a reusable heterogeneous catalyst for the synthesis. This new synthetic approach has good and fast conversion, robust conditions, and neat reaction profiles. The catalyst used is recyclable, insoluble in practically all solvents, and filtered out from the reaction media (Katla et al. 2016).



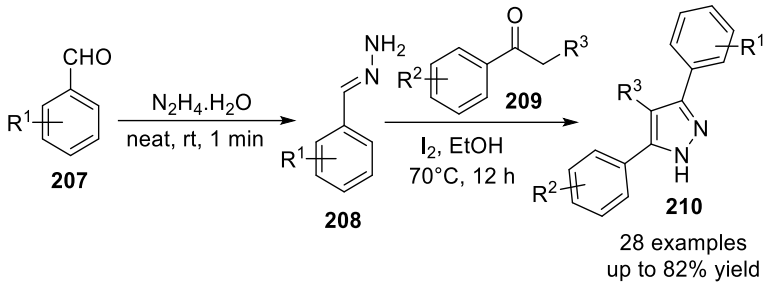
Scheme 1.50

Prisca Fricero and co-workers in 2017 proved that the pyrazole 5-trifluoroborates could be obtained through regioselective condensation of hydrazines and ynone trifluoroborates. The chemo-selective halogenation of the heteroaromatic ring is enabled by the stability of the borate unit, resulting in pyrazole scaffolds that allow orthogonal functionalization at C5 and C4. Cross-coupling reactions reveal the modular reactivity of these intermediates, providing the regio-controlled synthesis of fully functionalized pyrazole derivatives (Fricero et al. 2017).



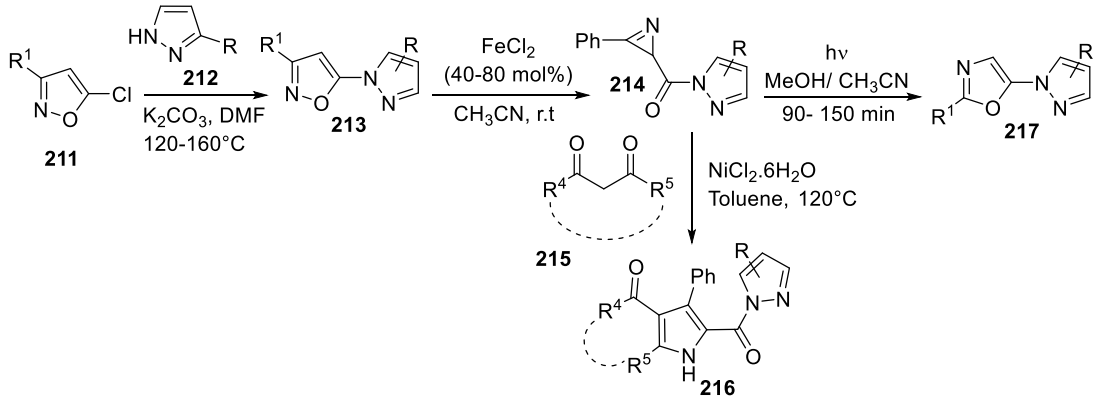
Scheme 1.51

Balakrishna Aegurla and his group, in 2017 introduced the iodine-mediated diaza-Nazarov (DAN) type cyclization to produce substituted pyrazoles from readily available starting materials. Under green conditions, the oxidative cyclization operated via an enamine–iminium ion intermediate exhibited remarkable regioselectivity. The substrate scope of this one-pot, efficient, and operationally easy three-component intramolecular regioselective DAN cyclization was quite broad. The ease of the experimental approach and the readily available starting materials make this an appealing strategy (Aegurla and Peddinti 2017).



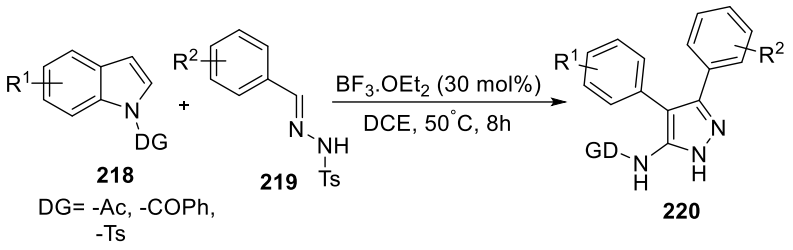
Scheme 1.52

Synthesis of pyrazole – nitrogen heterocycle dyads via the in situ trapping of 2H-azirine-2-carbonylchlorides produced by Fe(II)-catalyzed isomerization of 5-chloroisoxazoles with pyrazoles were developed by Kirill I. Mikhailov et al. in 2018. The DFT calculations proved that the thermodynamic parameters affect the selectivity of nucleophilic substitution at the carbonyl group of 2H-azirine-2-carbonylchloride . The two pyrazole-nitrogen heterocycle dyads, 5-(1Hpyrazol-1-yl)oxazoles and 1-(1H-pyrrol-2-ylcarbonyl)-1H-pyrazoles were prepared by photolysis and via Ni(II) catalyzed reaction with 1,3-dicarbonyl compounds. In acetonitrile, 5-(1H-pyrazol-1-yl)oxazoles emit strongly at 360-410 nm with good quantum yields (Mikhailov et al. 2018).



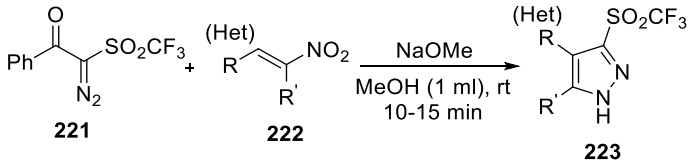
Scheme 1.53

Subhankar Panda and co-workers developed a novel aromatic ring-opening approach for converting indoles to pyrazoles in 2018. The ability of the N-acyl (or tosyl/benzoyl) indole to form complexes with the Lewis acid, according to mechanistic research, is what drives the ring-opening reaction (Panda et al. 2018).



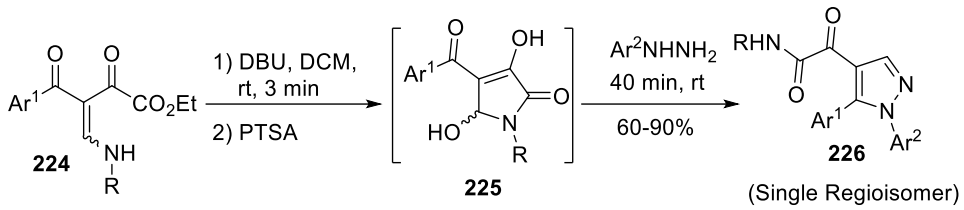
Scheme 1.54

Pulakesh Das et al. disclosed the procedure to make pyrazole triflones with a triflyl group at the 3-position. Under basic conditions, treatment of 2-diazo-1-phenyl-2 ((trifluoromethyl)sulfonyl)ethan-1-one with nitroalkenes yielded pharmaceutically appealing pyrazole 3-triflones in good to high yields. Almost all the nitrostyrene derivatives containing electron-donating, electron-withdrawing, and halogenyl substituents at different positions on the benzene ring, irrespective of the electronic nature and steric effects, provided the corresponding pyrazole triflones in good to high yields. The researchers then tested the reaction of a non-fluorinated analogue, 2-diazo-1-phenyl-2-(methanesulfonyl) ethenone with nitrostyrene under the optimized reaction conditions to verify the involvement of the CF_3 group in the cyclization reaction. The poor yield of the product generated demonstrates the benefit of the SO_2CF_3 moiety in this cyclization reaction (Das et al. 2018).



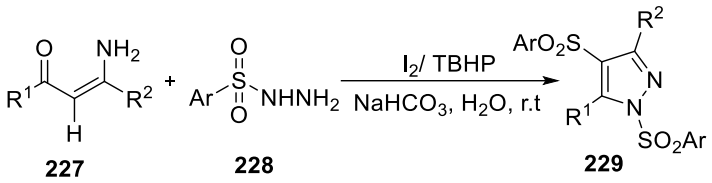
Scheme 1.55

The synthesis of highly regioselective α-ketoamide N-arylpyrazoles from secondary -enamino diketones is disclosed using an efficient one-pot technique by Julia Poletto and co-workers. The crucial intermediate, 4-acyl 3,5-dihydroxypyrrolone, was synthesized in situ, which undergoes nucleophilic substitution at the C-5 position by arylhydrazine, followed by heterocyclization at the acyl group's carbonyl carbon. The freshly synthesized pyrazole's structures and regiochemistry were validated using spectroscopic and analytical data. The X-ray crystal structure of pyrazole offered definite structural proof for regiochemistry (Poletto et al. 2019).



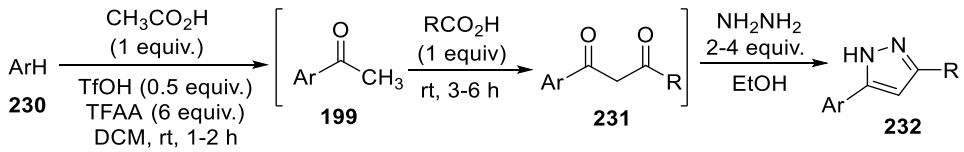
Scheme 1.56

Yanhui Guo et al. in 2019 reported the synthesis of highly substituted pyrazoles via cascade reactions involving NH_2-functionalized enaminones and sulfonyl hydrazines. The reactions proceed efficiently in pure water in the presence of molecular iodine, TBHP, and $NaHCO_3$ via cascade C-H sulfonylation and pyrazole annulation. The dissociation of the C-N bond in enaminones is confirmed by the ^{15}N-labeled enaminone experiment (Guo et al. 2019).



Scheme 1.57

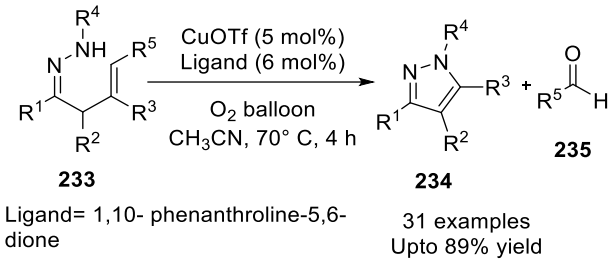
A rapid and efficient approach for the one-pot synthesis of pyrazoles from (hetero)arenes and carboxylic acids was established by Jung Keun Kim and his group in 2020. The reaction involves the production of ketones, 1,3-diketones, followed by the heterocyclization with hydrazine. The fundamental characteristic of this strategy is the use of RCOOH/TfOH/TFAA acylation system for the intermediate synthesis of ketones and 1,3-diketones. The procedure was improved to generate trisubstituted and condensed pyrazoles. The heterocyclization of benzhydrol α- alkylated β- diketones resulted in a four-step one-pot synthesis of 3,4,5-trisubstituted pyrazoles. The antitumor activity of produced pyrazoles was also evaluated at the preclinical stage (Kim et al. 2020).



Scheme 1.58

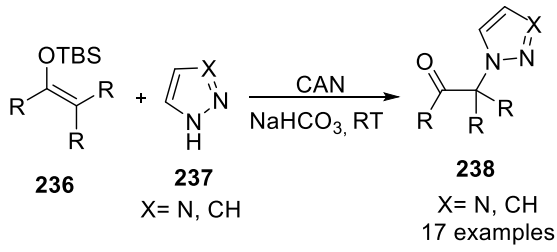
The synthesis of pyrazole derivatives has been achieved using a Cu-catalyzed aerobic oxidative cyclization of β,γ-unsaturated hydrazones by Zhenwei Fan et al. The

cyclization was aided by the hydrazonyl radical, which also caused the cleavage of the β, γ-unsaturated hydrazones' C=C bonds. Oxygen was used as the terminal oxidant in this method, while a low-cost Cu (I) salt was used as the catalyst. This Cu-catalyzed aerobic oxidative transformation was notably synthetically beneficial, practical, and green due to its operational simplicity and mild reaction conditions, combined with a more general functional group tolerance. Several control studies, including radical-trapping research, an ^{18}O labeling method, and the detection of potential byproducts, have been used to verify this procedure (Fan et al. 2020).



Scheme 1.59

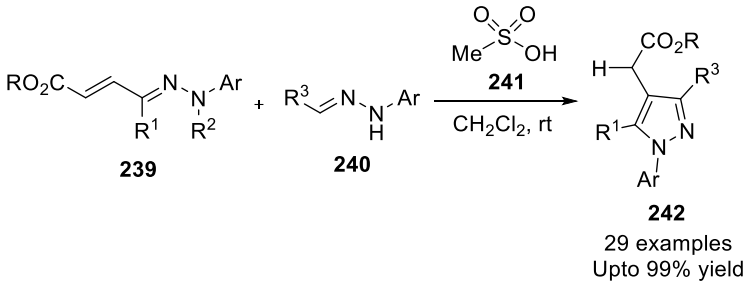
Sandeep Dhanju and his group in 2020 reported the ceric ammonium nitrate (CAN-$Ce(NO_3)_6(NH_4)_2$)-mediated oxidative coupling of enol silanes with heteroarenes to synthesize α-pyrazole and α-triazole derivatives of ketones. As a precursor to the radical-cation intermediate, initially, they used tert-butyldimethylsilyl enol ether and 1H-pyrazole as the nucleophile. Over 20 minutes, enol ether was added to a stirred CAN solution to avoid a substantial formation of the unwanted 1,4-diketone adduct of silyl enol ether dimerization. Both cyclic and acyclic enol ethers produced the necessary compounds in good to outstanding yields. Specifically, sterically demanding -pyrazole ketones were synthesized, including fully substituted carbon centres (Dhanju et al. 2020).



Scheme 1.60

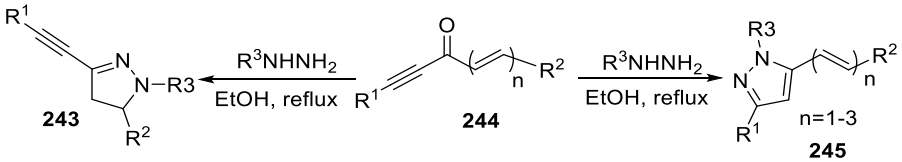
The β-protonation/nucleophilic addition/cyclization/aromatization sequence was designed to synthesize pyrazoles from conjugated hydrazones using the Bronsted acid-

mediated method by Haruo Matsuzaki et al. The reaction with methanesulfonic acid at room temperature yielded the required pyrazole in good yield. According to preliminary testing, CH_2Cl_2 was the best acceptable solvent for this condensation process among the various solvents screened. By synthesizing the nonsteroidal anti-inflammatory drug Lonazolac, they demonstrated the utility of this cross-condensation. This procedure, which makes use of hydrazones' amphiphilic reactivity, allows for cross-condensation and self-condensation (Matsuzaki et al. 2020).



Scheme 1.61

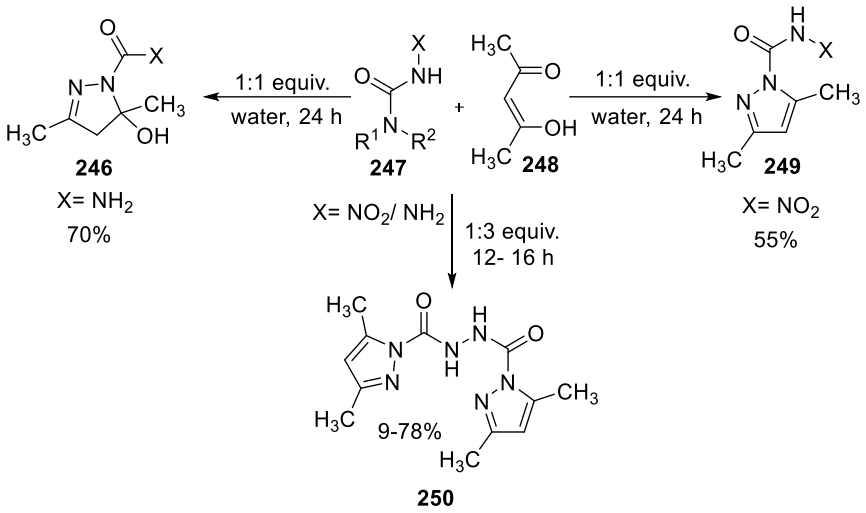
Alexander A. Golovanov and his group developed the regioselective synthesis of 4, 5-dihydro-1H-pyrazoles when cross-conjugated enynones, dienynones, and trienynones are cyclocondensed with arylhydrazines. The character of the substituent in enynone controls the reaction path: pyrazoles are consistently obtained from the reaction of 1,5-diphenylpent-1-en-4-yn-3-one with arylhydrazines, and 4,5-dihydro-1H-pyrazoles are consistently obtained from the reaction of 1,5-diphenylpent-1-en-4-yn-3-one with arylhydrazines. Regardless of the existence of a substituent, cyclo condensation of 2-hydrazinylpyridine with all of the cross-conjugated enynones studied results in the generation of pyrazoles (Golovanov et al. 2021).



Scheme 1.62

The reaction of semicarbazide and 4-nitrosemicarbazide with acetylacetone is proposed as a new method to obtain pyrazole derivatives by Vera S. Glukhacheva et al. The reaction with acetylacetone yielded monocyclic 3,5-dimethyl-N-nitropyrazole-1-carboxamide, monocyclic 5-hydroxy-3,5-dimethyl-2-pyrazoline, and bicyclic bis(3,5-dimethylpyrazole-1-carbonyl) hydrazine. Physicochemical analytical procedures, such

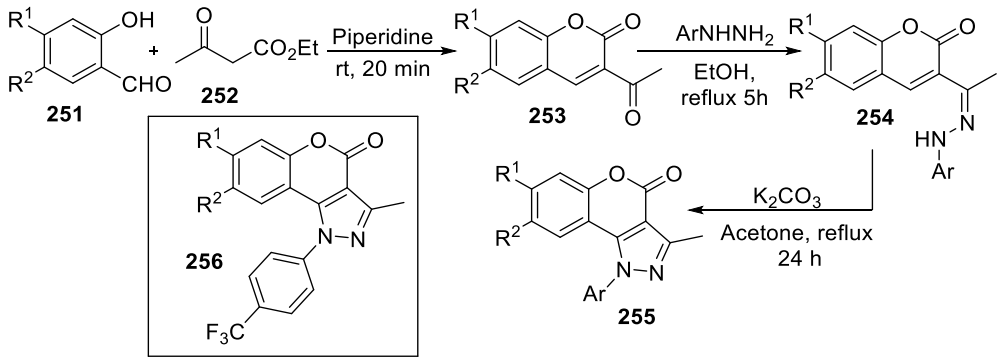
as X-ray diffraction, were used to confirm the structures of the resulting compounds. According to computer-aided screening in the PASS prediction software, the newly obtained compounds had a high biological activity (Glukhacheva et al. 2021).



Scheme 1.63

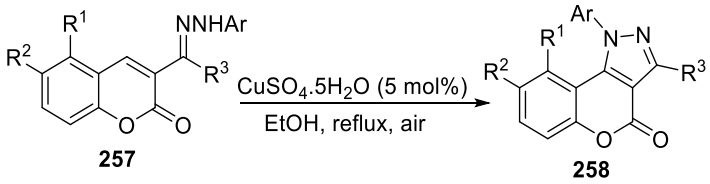
Part B: This section covers a brief literature report on the various synthetic methods towards Chromenopyrazoles and their derivatives.

The in vitro COX inhibitory ability of a series of 3-methyl-1-phenylchromeno[4,3-c]pyrazol-4(1H)-ones were investigated by Jagdeep Grover and co-workers in 2014. The synthetic steps include Knovenagel condensation of salicylaldehyde and ethyl acetoacetate. Acetyl coumarin generated produces 3-[1-(phenylhydrazono)-ethyl]-chromen-2-ones by reacting with various phenyl hydrazines. Finally, the 3-[1-(phenylhydrazono)-ethyl]-chromen-2-ones undergo base-mediated intramolecular cyclization to produce the target compounds. According to structure-activity relationship studies, the N-phenyl ring substituted with the p-CF_3 substituent leads to more selective suppression of COX-2. Molecular docking research was conducted, which found that compound **256** had a more excellent binding relationship with COX-2 than COX-1 (Grover et al. 2014).



Scheme 1.64

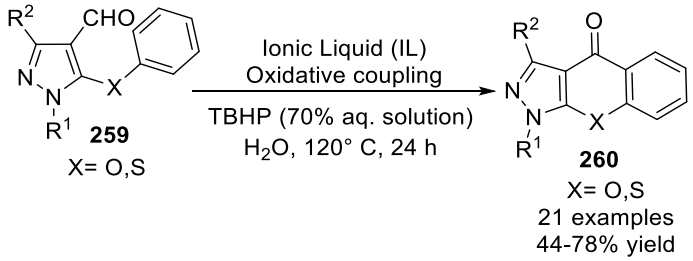
Hui-Yan Wang and his colleagues disclosed an effective and practical Cu-catalyzed synthesis of chromeno[4,3-c]pyrazol-4(1H)-ones. In this atom-saving procedure, abundantly available 3-acylcoumarin hydrazone is oxidatively cyclized by forming a straight C–N link. Only a trace product was discovered when the reaction was carried out without a catalyst. The use of air as an oxidant has proven successful, with significant economic and environmental benefits. A wide range of substrates can be used in the process, with moderate to high yields. Accessible materials, mild reaction conditions, operational simplicity, clearer reaction profiles, and greater yields are advantages of this approach (Wang et al. 2015).



Scheme 1.65

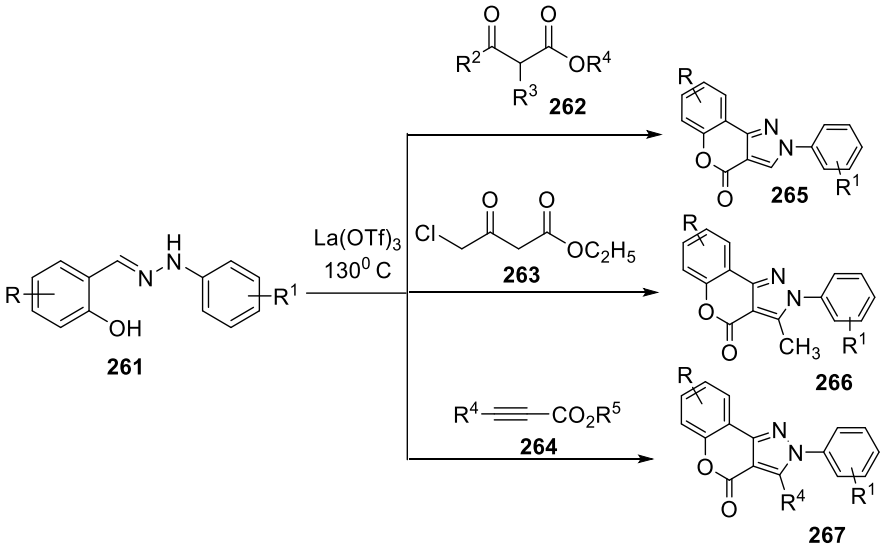
The intramolecular annulation of 5-(aryloxy)-1H-pyrazole-4-carbaldehydes to chromeno[2,3-c]pyrazol-4(1H)-ones have been reported using the first classical heterocyclic ionic liquid (IL) assisted C-H bond cross-coupling reaction by He Li et al. Different kinds of ionic liquids were added to the reaction system. Indeed, IL5 1,3-dibutyl-1H-benzo[d]-[1,2,3]triazol-3-ium bromide ([Dbbta]Br) exhibited a more positive influence on the reaction. The aryloxy portions with electron-withdrawing groups were generally more reactive than those with electron-donating groups, resulting in higher yields. Surprisingly, the yield was unaffected by substituents at the ortho position of the aryloxy group. In aqueous media, the promoter 1,3-dibutyl-1H-

benzo[d][1,2,3]- triazol-3-ium bromide can be easily recycled and reused for at least five cycles with the same efficacies (Li et al. 2015).



Scheme 1.66

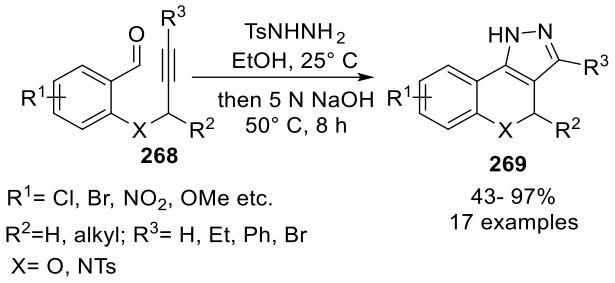
The reaction of salicylaldehyde phenylhydrazones with β-ketoesters and activated alkynes in the presence of $La(OTf)_3$ has been developed as a simple, solvent-free methodology for the production of chromenopyrazolones with a high yield. Compared to other Lewis acids, $La(OTf)_3$ gave a higher yield for the compound. Salicylaldehyde phenylhydrazones were cyclized with ethyl 4-chloro-3-oxobutanoate by reductive dechlorination, yielding methyl chromenopyrazolones rather than chloromethyl chromenopyrazolones (Hariprasad et al. 2016).



Scheme 1.67

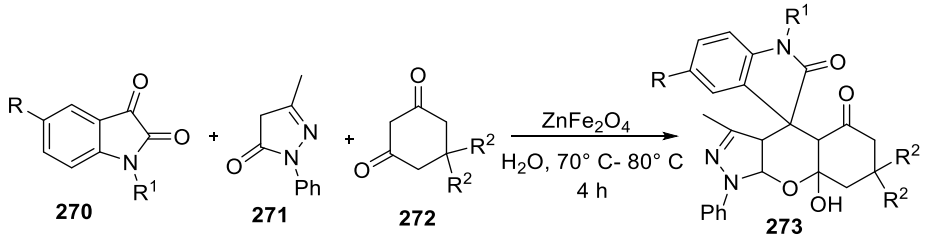
From readily available precursors, one-pot synthesis of highly substituted pyrazoles coupled to dihydrochromenes, dihydroquinolines, and cyclopentane motifs was disclosed by K. Vijay L. Divya and co-workers. The approach allows the generation of pyrazolo-dihydrochromenes with various substituents at specific locations. Different internal and terminal alkynes and bromoalkyne compounds can be used as the tethered

dipolarophile to obtain the cycloadducts. The approach can also be utilized to make pyrazolo-dihydroquinoline derivatives and cyclopentane-fused pyrazole (Divya et al. 2016).



Scheme 1.68

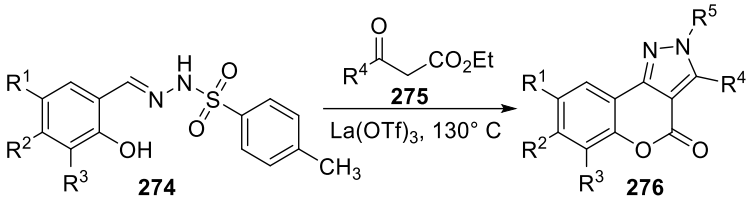
The reaction of substituted isatins, cyclic-1,3-diketones, and 1-phenyl pyrazolone in the presence of nanopowder catalyst and water as reaction medium has been described by Kajal De et al. as an improved environmentally benign one-pot three-component approach for the synthesis of pyrazole-fused chromene derivatives. The spinel zinc ferrite nanopowder catalyst, which provides dual catalytic active sites, was synthesized using a low-temperature preparative approach. Initially, in the presence of Zinc ferrite nanopowder, substituted isatins react with 1-phenylpyrazolone resulting in a Knoevenagel condensation product that coordinates with the Fe^{3+} atom of the Zinc ferrite framework to facilitate the reaction further. To build up the mechanism for developing pyrazole-combined chromenes, the group separated the intermediate from the reaction of allyl isatin,1- phenyl pyrazolone, and 4,4-dimethyl cyclohexane-1,3-dione at distinctive time stretches. This method effectively constructs various pyrazole-fused chromene frameworks from commonly available commercial chemicals and straightforward synthesis methods (De et al. 2017).



Scheme 1.69

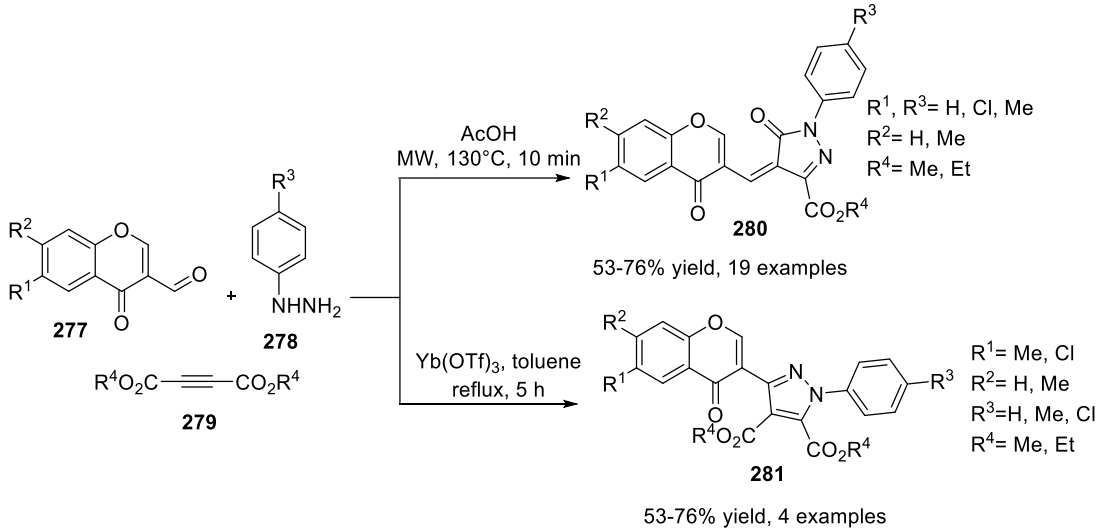
Kurma Siva Hariprasad and co-workers developed a method to synthesize chromenopyrazolones, tosylchromenopyrazolones, and benzoylcoumarins from

salicylaldehyde tosylhydrazones and 3-oxobutanoates. The electron-donating substituents such as methyl and methoxy salicylaldehyde tosylhydrazones did not provide the compounds under the reported conditions. The trifluoromethyl chromenopyrazolones were found to have antimicrobial action in bioactivity profile tests. This was the first publication on the structure-activity relationship of chromenopyrazolones and benzoylcoumarins in antimicrobial and anti-inflammatory inhibitory properties (Hariprasad et al. 2017).



Scheme 1.70

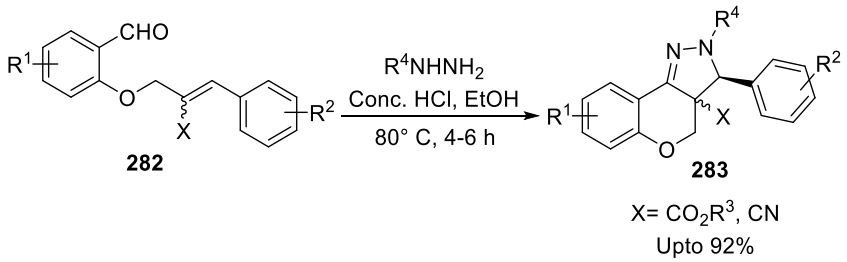
The three-component reactions of 3-formylchromones, arylhydrazines, and acetylenedicarboxylates were presented as a simple way to get hybrid bioactive compounds like chromenopyrazoles by Paraskevi M. Kasapidou and co-workers in 2017. Four alternative scaffolds can be easily, versatilely, and robustly generated by modifying the reaction. Representative libraries of each scaffold were generated to highlight the potential, generality, and diversity of the developed strategy(Kasapidou et al. 2017).



Scheme 1.71

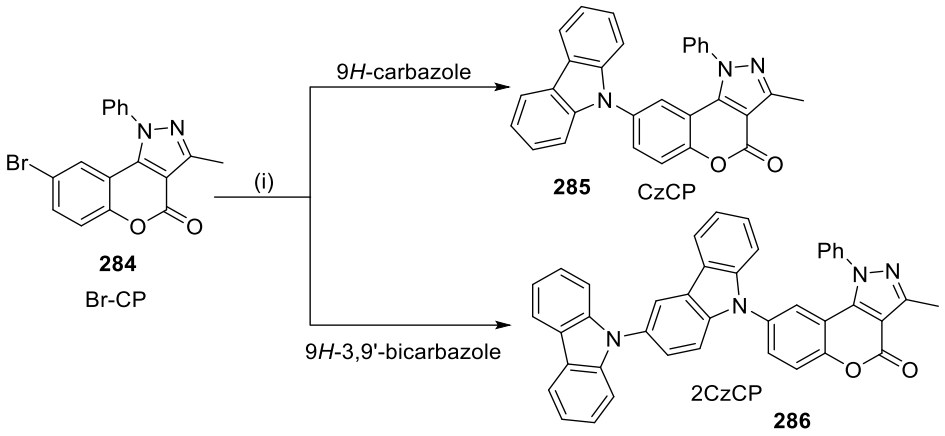
For the first time, Manickam Bakthadoss et al. reported an intramolecular azomethine imine 1, 3-dipolar cycloaddition (IAIDC) reaction of O-allylated salicylaldehydes and

aryl hydrazines to produce angularly substituted tricyclic chromenopyrazoles. NMR spectra and X-ray crystal studies demonstrated the great diastereoselectivity, and stereospecificity in producing quaternary functionalized tricyclic chromeno- fused pyrazole frameworks. The production of two rings and two contiguous stereogenic centers, one of which is an all-carbon quaternary center, are additional unique properties of this protocol. The fluorescent properties of the newly synthesized compounds were investigated, and some of the compounds were discovered to have strong fluorescent capabilities (Bakthadoss and Agarwal 2018).



Scheme 1.72

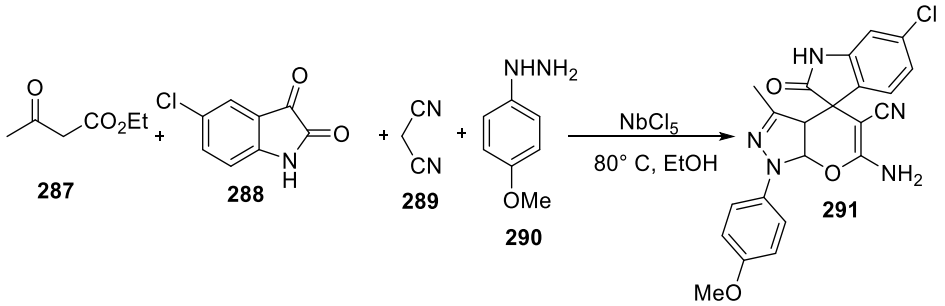
Mallesham Godumala et al. employed chromenopyrazole (CP) as an electron-acceptor core for the first time to develop and manufacture two novel blue bipolar hosts, namely, 8-(9*H*carbazol- 9-yl)-3-methyl-1-phenylchromeno[4,3-c]pyrazol-4(1*H*)-one (**CzCP**) and 8-(9*H*-[3,9'-bicarbazol]-9-yl)-3-methyl-1- phenylchromeno[4,3-c]pyrazol-4(1*H*)-one (**2CzCP**). The starting compound Br- CP used for the reaction was synthesized by the Knovenagel condensation reaction between ethyl acetoacetate and 5- bromo salicylaldehyde followed by condensation with phenylhydrazine and intramolecular cyclization. Br- CP is then subjected to Buchwald– Hartwig coupling reaction in presence of palladium acetate to generate the designed compounds CzCP (**285**) and 2CzCP (**286**). The effect of donor strength on photophysical, electrochemical, and electroluminescent properties was studied in depth. With an external quantum efficiency of 27.9% and CIE color coordinates of (0.15, 0.21), OLEDs containing CzCP as a host in the emissive layer achieved excellent performance among reported blue host materials in TADF-OLEDs (Godumala et al. 2018).



(i) K_3PO_4, $Pd(OAc)_2$, $P(t\text{-}Bu)_3$, toluene, reflux.

Scheme 1.73

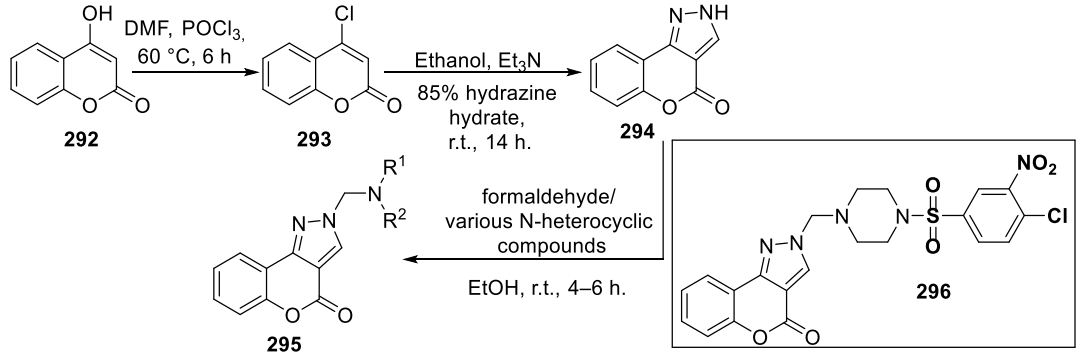
A new green approach for the synthesis of a set of pharmaceutically significant spiro pyrazole and benzo[7, 8] chromene derivatives was developed by Vairaperumal Veeramani and the research group. In a one-pot four-component approach, these derivatives were made by reacting various substituted isatins with ethylacetoacetate, 2-hydroxy-1,4-naphthaquionone/malonitrile, and hydrazines or phenylhydrazine in the presence of different catalysts. The multi-component reactions utilized a variety of Lewis acids as catalysts and polar solvents as reaction media (MCRs). $NbCl_5$ and ethanol were the most effective catalyst and solvent, respectively, among the several catalysts and solvents tested. FT-IR, 1D, and 2DNMR spectroscopy methods confirm the produced molecules. The group succeeded in synthesizing several new biologically relevant spiro pyrazole and benzo[7,8]chromene derivatives with similar cores to many natural compounds with medicinal significance (Veeramani et al. 2018).



Scheme 1.74

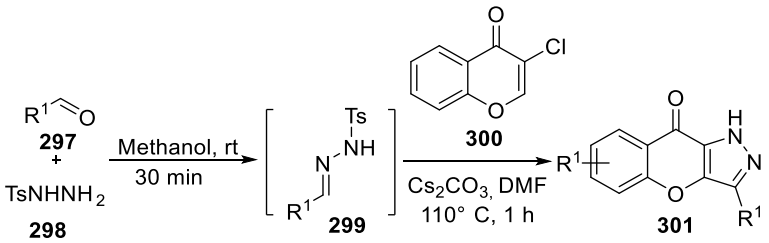
Yong Yin and his team synthesized piperazine-containing chromeno[4,3-c]pyrazol-4(2H)-one derivative. The synthesis steps start with the classic Vilsmeier- Haack reaction followed by the cyclization of 4-chloro-2H-chromen-2-one with hydrazine

hydrate. Further, the final compounds were attained by treating chromeno[4,3-c]pyrazol4(2H)-one with formaldehyde and various nitrogen-containing heterocycles. Their inhibitory activities and anticancer effects against PI3K wild-type and H1047R mutants were assessed in vitro. Compound **296**, in particular, showed excellent antiproliferative activity and appeared to be a promising PI3Kα inhibitor(Yin et al. 2019).



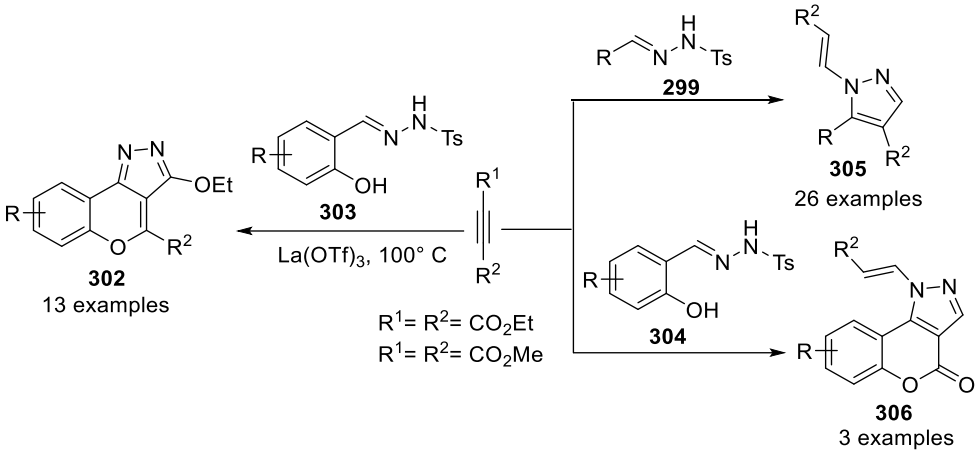
Scheme 1.75

The chemoselective synthesis of monocyclic/tricyclic-fused pyrazoles was created by Tianzi Dai and the group using a simple and efficient synthetic method oriented by distinct 3-position substituents (H or Cl) on the chromones. The reaction proceeded in one-pot sequential with a broad substrate scope and moderate to exceptional yields. They moved on to tricyclic chromeno[3,2-*c*]Pyrazoles after successfully synthesizing monocyclic pyrazoles from 3-unsubstituted-chromones. The efficiency was considerably influenced by the electronic characteristics of chromone ring substituents, with electron-donating groups displaying better reactivity in terms of isolated yields. When an aliphatic aldehyde like cyclohexanaldehyde was utilized, a lesser yield was attained, and many ring-opening byproducts were created simultaneously (Dai et al. 2019).



Scheme 1.76

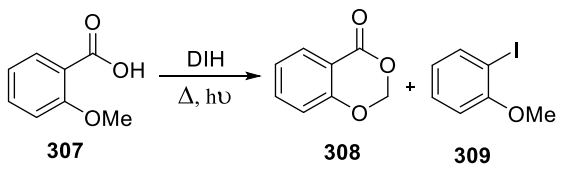
The reaction of N-tosylhydrazones and salicyl N-tosylhydrazones with alkynes under the neat conditions in the presence of $La(OTf)_3$ yielded a highly regio- and stereoselective approach for the production of N-alkenylpyrazoles and chromenopyrazoles. Siva Hariprasad Kurma and co-workers used N′-benzylidene-4-methylbenzenesulfonohydrazide, made from benzaldehyde 4-methylbenzenesulfonohydrazide, as a model substrate to establish the reaction conditions. The current approach entails the synthesis of five-membered heterocyclic compounds, including a fused one, in a single pot using C-C, two C-N, and C-O bond formation processes (Kurma et al. 2021).



Scheme 1.77

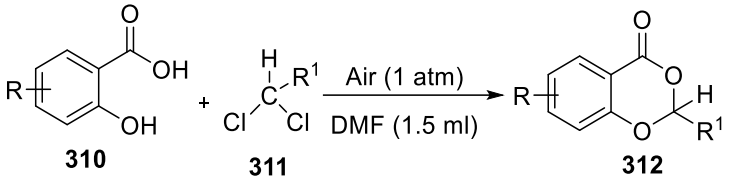
Part C: This section covers a brief literature report on the various synthetic methods towards Benzodioxinones and their derivatives.

Kseniya Kulbitski *et al.* (2011) reported a metal-free novel and robust method for the conversion of carboxylic acid to benzodioxinone and iodo-organic compound using N-iodoamides. The transformation applies to primary, secondary, and tertiary alkanoic and aromatic carboxylic acids, yielding a non-toxic and straightforward product. Commercially available N-iodoamides were incorporated for both initiation and halogenation under irradiative conditions. Isolation of the product was even more straightforward as the co-product remove as a water-soluble, biodegradable material (Kulbitski et al. 2011).



Scheme 1.78

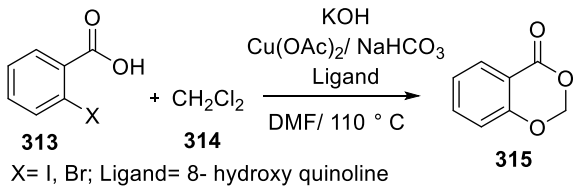
Feng Lin et al. have developed an ecologically practical method to construct 4H-benzo [d] [1, 3] dioxin-4-one and its derivatives, which are essential for pesticides and an intermediate to synthesize high-value multi-substituted benzene derivatives. Variously substituted benzene rings tolerated the reaction well and delivered outstanding yields under conventional reaction conditions. Substituents at the ortho-, meta-, and para-positions of the aromatic moiety had no significant effect on the outcome in this series of studies. The cyclized product was further transformed into salicylic acids, salicylate esters, 7-(Bromomethyl)-4H-benzo[d][1,3]dioxin-4-one, 2- (hydroxymethyl)phenol, etc. via some conventional reactions. The absence of catalysts and additives, commercial and low-cost starting materials, and a fast reaction time make this process environmentally friendly, practical, and appealing (Lin et al. 2014).



310 311 312

Scheme 1.79

$Cu(OAc)_2$ was used by Yunyun Liu et al. to catalyze the reactions of o-halobenzoic acids, dichloromethane, and potassium hydroxide to produce benzo[d][1,3]dioxin-4-ones. The reaction of o-iodobenzoic acid with dichloromethane was investigated using KOH as the hydroxyl source under various reaction conditions. The desired product was not formed without the copper catalyst and base additive. Using o-iodo- and o-bromobenzoic acids, diverse structures were synthesized effortlessly. They further demonstrated that the Ullmann-type hydroxylation process could synthesize more structurally varied chemical compounds(Liu et al. 2017).



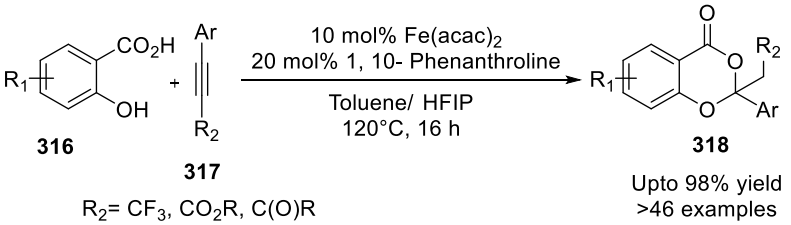
313 314 315

X= I, Br; Ligand= 8- hydroxy quinoline

Scheme 1.80

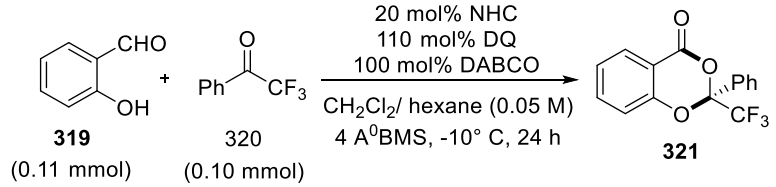
Taro Sonehara and co-workers demonstrate the iron-catalyzed intermolecular coupling of internal alkynes and thiosalicylic acid derivatives. The reaction was effectively

catalyzed by the $Fe(acac)_2$/1,10-phenanthroline catalyst in toluene/HFIP solvent system. The reaction described afforded several 1,3-oxathiine derivatives in moderate to high yields through the intermolecular hydrothiolation and sequential intramolecular cyclization (Sonehara et al. 2017).



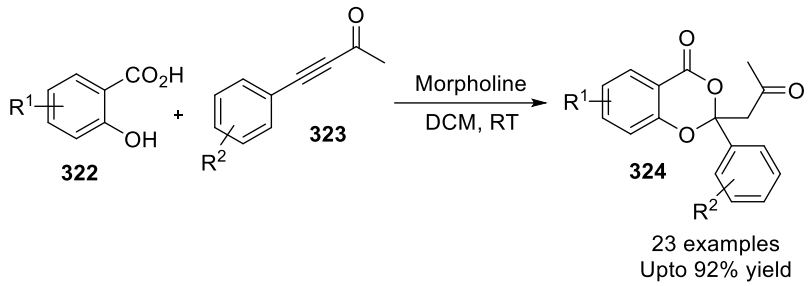
Scheme 1.81

A reaction mode of carbene-catalyzed activation of aryl aldehydes was used to produce a 1,3- benzodioxinone derivatives by Xingkuan Chen et al. in 2017. The carbene catalyst is added to the aldehyde moiety, which results in proximal phenol OH activation and dearomatization. An NHC-bound intermediate (o-QMs) is used in the catalytic reaction, with the oxygen atom acting as the reactive center. The NHC catalyst operates in combination with a hydrogen-bond donating co-catalyst (urea or thiourea), resulting in a significant and consistent increase in enantioselectivity. The reaction notably proves the power of carbene catalysis in asymmetric chemical synthesis (Chen et al. 2017).



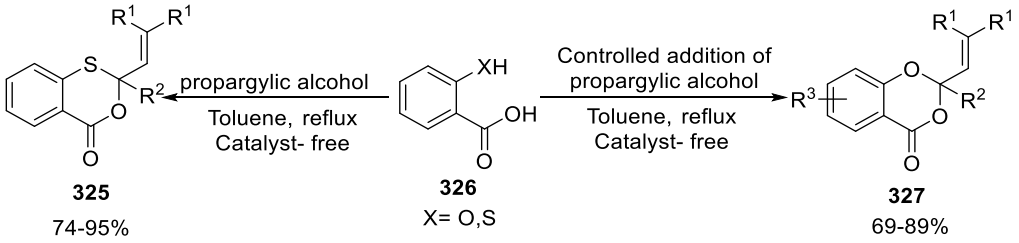
Scheme 1.82

Secondary amine-catalyzed dual Michael cascade reactions yielded a class of useful 4H-benzo[d][1,3]dioxin-4-ones. Several substituted salicylic acids were initially investigated. Secondary amines, such as morpholine, were found to be an effective catalyst for the commencement of the enamine activation pathway. The crucial intermediate in the cascade process, the α, β-unsaturated ketone, was also isolated successfully. (He et al. 2018).



Scheme 1.83

Sengodagounder Muthusamy et al. reported the reaction of propargylic alcohols and salicylic/thiosalicylic acids under a catalyst-free and open-air atmosphere that unambiguously yields 3,1-benzoxathiin-4-ones/1,3-benzodioxin-4-ones. Several transition metals were screened to promote the hydrothiolation - intramolecular cyclization sequence. The reaction starts with the formation of a propargylic cation which follows tautomerism to produce an allenic cation. The features such as ready availability of substrates, robust conditions, and operational simplicity were beneficial for the large-scale applications of the reaction (Muthusamy et al. 2021).



Scheme 1.84

1.5 SCOPE AND OBJECTIVES

Heterocycles, particularly nitrogen and oxygen-based heterocycles, are unique scaffolds with numerous applications in almost all chemistry, biology, and material science disciplines. The synthesis of these heterocycles, such as pyrazole, imidazole, coumarin, pyrimidinone, dioxinones, isoxazoles, and benzimidazoles, was both appealing and challenging to chemists because these core structures have a wide range of applications in material science, analytical chemistry, and most importantly, medicinal chemistry (Gulati et al. 2021). The widespread applications of pyrazoles, chromenopyrazoles, and benzodioxinones in various fields, ranging from therapeutics to fluorophores to industry products, always attracted synthetic organic chemists to develop new and efficient methods towards these moieties through various approaches.

The 1, 3-dipolar cycloaddition of diazoalkanes or nitrilimines with olefins or alkynes is the most widely used protocol to synthesize pyrazole, though the reactivity and stability of various 1, 3-dipoles still pose some challenges. Many other reaction pathways are also present, which requires pre-functionalized substrates, vigorous conditions, sensitive reagents, and prolonged time. Hence efficient and simple routes towards developing pyrazole are always noteworthy as the scaffold is essential in drug development and material chemistry. Benzodioxinone and its derivatives are potentially active core in pharmaceuticals and pesticides. Synthetic routes reported in the literature for this active core involve pre-functionalized substrates, harsh conditions, expensive catalysts, and sensitive reagents. Improvised synthetic methods to benzodioxinones always attracted organic chemists. Against this background, it has been planned to design and develop efficient synthetic routes to construct molecular scaffolds of high diversity, which can be used for a later stage functionalization. The scope of these reactions is broad and offers excellent functional group tolerance, and can be applied to a wide range of substrates to synthesize pyrazole, chromenopyrazole, and benzodioxinone based molecular library. The primary objectives of the present work are,

1) Development of efficient synthetic methods towards the synthesis of pyrazoles, chromenopyrazoles and benzodioxinones via dipolar cycloaddition and oxa-Michael addition strategy.
2) To carry out further functionalization of the synthesized heterocycles to prove the synthetic utility of the molecules.
3) To purify the synthesized molecules by column chromatography and recrystallization techniques.
4) To characterize the new molecules using spectroscopic methods (FT-IR, ^{1}H NMR, ^{13}C NMR, Mass spectroscopy, and CHN Analyzer) and to deduce the crystal structure of representative molecules using Single-crystal XRD.

1.6 THESIS FRAMEWORK

The present research work has been divided into six chapters; details of each are given below:

Chapter 1 introduces the broad area of the research work. A brief introduction to dipolar cycloaddition reactions and the oxa-Michael addition reactions is included, followed by a detailed literature study on various synthetic approaches towards pyrazoles, chromenopyrazoles, and benzodioxinones. This chapter concludes with an outline of the scope and objectives of the present research problem.

Chapter 2 is on the metal-free synthesis of pyrazoles from hydrazones and acetylenic esters. This includes a brief introduction and applications of pyrazoles, the materials and methods used in the work, experimental procedure, optimization table, synthetic scheme and derivatives, and a brief description of the characterization techniques used. This chapter also includes detailed characterization data of all the synthesized compounds.

Considering the proximity of the ester and hydroxyl groups in the pyrazole resulting from salicylaldehyde hydrazone and acetylenic esters, we carried out a heating reaction of these substrates in TFA to generate chromenopyrazoles. This robust, step-economic, one-pot cyclization is described in **Chapter 3**. The work includes methodology and derivatives synthesized, followed by characterization data.

The reactivity of activated olefins towards the dipolar cycloaddition reactions to aldehyde hydrazones is studied in **Chapter 4**. The discussions in this chapter focus on optimizing the reaction conditions, the substrate scope of the reaction and the synthesis of variously substituted pyrazoles from electronically different hydrazones and activated alkenes. The synthesized pyrazole derivatives are characterized by FT-IR, ^{1}H NMR, ^{13}C NMR, and HRMS/ LCMS analysis.

Chapter 5 is about oxa-Michael addition-based intramolecular cyclization mediated by Cu(I), resulting in the benzodioxinones and their direct amidation at room temperature. The chapter includes a brief introduction of benzodioxinones followed by the experimental section, optimization table, substrate scope, and characterization.

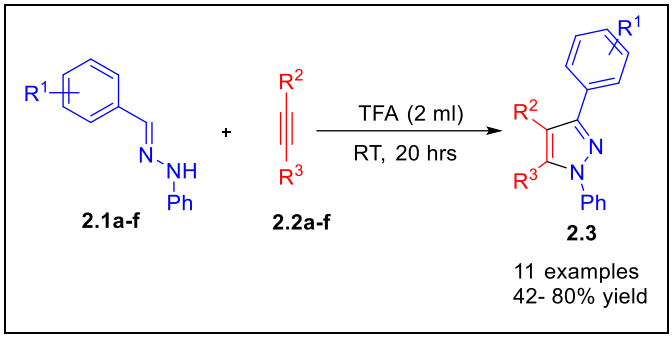
The summary and outcome drawn from each chapter conclude the thesis in **Chapter 6**.

CHAPTER 2

METAL-FREE SYNTHESIS OF PYRAZOLES FROM HYDRAZONES AND ACETYLENIC ESTERS

Abstract

An acid mediated metal-free approach towards the synthesis of pyrazoles from hydrazones and acetylenic esters at room temperature is described. The developed strategy shows excellent functional group tolerance. A library of molecules with diverse functional groups has been synthesized using substituted hydrazones and alkynes, both symmetrical and unsymmetrical ones.



2.1 INTRODUCTION

Pyrazole, the nitrogen-containing five-membered heterocycle, is an important structural motif in numerous compounds due to their potential applications in diverse fields of chemistry such as pharmacological, agricultural, material and analytical chemistry. Pyrazole is a chemist-developed versatile starting chemical for the production of therapeutically active compounds. The widespread presence of pyrazole cores in clinically active compounds has prompted researchers to devise innovative, green, and economical methods for producing this heterocyclic molecule. Various substituted pyrazoles have also been discovered to be employed as chelating and extracting reagents for a variety of metal ions. The natural abundance of pyrazoles is limited, probably due to the difficulty associated with the N-N bond-formation. Nevertheless, synthetic chemists developed numerous synthetic routes to construct the pyrazole scaffold effectively over the decades. Especially, synthetic and medicinal chemists are more interested in pyrazole chemistry owing to their diverse properties.

Pyrazoles have a long history in chemistry; in 1883, a German chemist named Ludwig Knorr was the first to discover the antipyretic properties of a pyrazole derivative, which he called antipyrine. Antipyrine, which possesses analgesic, antipyretic, and antirheumatic action, was accidentally obtained when he synthesized quinoline

derivatives with antipyretic activity. They are categorized as alkaloids because of their structure and pharmacological effects on humans, despite their rarity in nature. Pyrazoles, once regarded as compounds with no natural origin, were isolated later. In 1954, Japanese researchers Kosuge and Okeda identified the first natural pyrazole derivative. The researchers isolated 3-nonylpyrazole from Houttuynia Cordata, a plant of the "*piperaceae*" family from tropical Asia, which shows antimicrobial activity. Later, *levo*-β-(1-pyrazolyl) alanine, an amino acid derivative, was identified from watermelon seeds. However, the natural resources remained very scares and the demand for pyrazoles is being satisfied by the diverse synthetic routes developed by synthetic organic chemists over the past few decades.

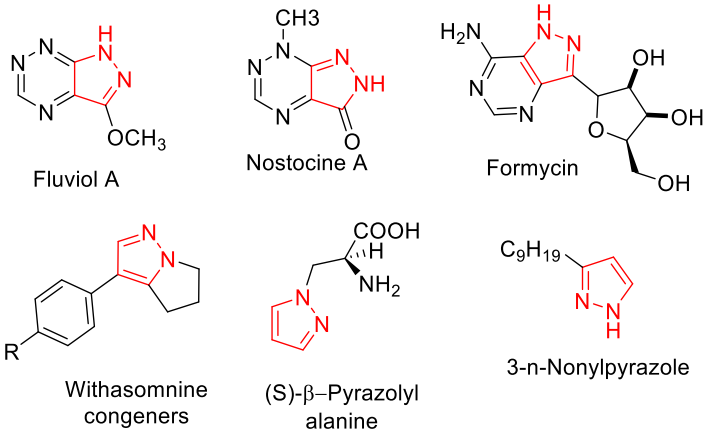


Figure 2.1 Pyrazole containing natural products

2.2 PYRAZOLES AND THEIR APPLICATIONS

Pyrazole is a five-membered π-excessive heterocycle with two nitrogen atoms at positions 1 (pyrrole type) and 2 (pyridine type). The N-H hydrogen of pyrazole is more acidic than that of pyrrole and hence can be deprotonated, while the pyridine-type nitrogen is susceptible to electrophilic attack. Pyrazole can be halogenated, nitrated, or sulphonated with ease.

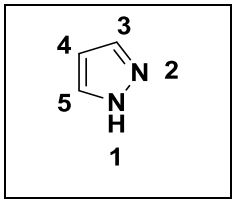


Figure 2.2 Structure of Pyrazole

Molecules with pyrazole core have been known to exhibit various biological actions, including anticancer, antitumour, anti-HIV, antibacterial, antimalarial, and antitubercular properties. The widespread applications of pyrazole scaffolds in drugs and pharmaceuticals are well known, and commercial drugs such as lonazolac (NSAID), pyrazofurin (anticancer), difenamizole (analgesic), and deracoxib (NSAID) are a few examples of the class. The pyrazole ring is a core component in several popular therapeutics, including celebrex, viagra, and rimonabant. Azo derivatives of pyrazoles are well known and widely used as CNS depressive, anticancer, and powerful local anesthetics. They have also been used in agricultural and pharmaceutical research as pesticides and repellents. Suitably functionalized pyrazoles serve as ligands for metal catalysis. Pyrazole and its derivatives are an attractive platform for chemical, medicinal, and pharmaceutical chemistry because of their ease of production and wide range of biological effects.

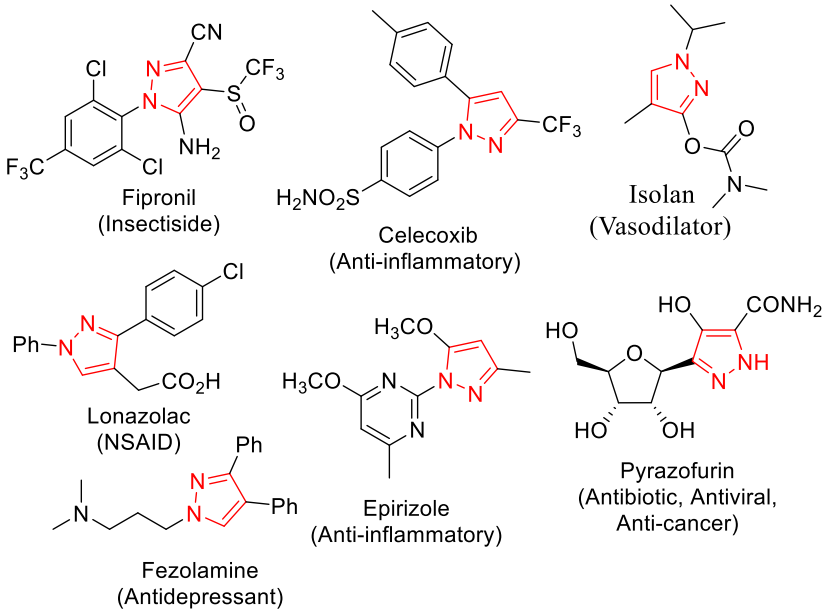


Figure 2.3 Drug molecules with pyrazole core

Renuka Nagamallu et al., in 2016, have synthesized a series of biologically interesting coumarin pyrazole hybrids via Vilsmeier Haack formylation reaction from hydrazones, carbazones, and thiocarbazones. The coumarin appended bis (formyl pyrazoles) formed were evaluated for antimicrobial and antioxidant activities. Compounds **1** and **2** were discovered to be powerful antioxidants (**Figure 2.4**) (Nagamallu et al. 2016).

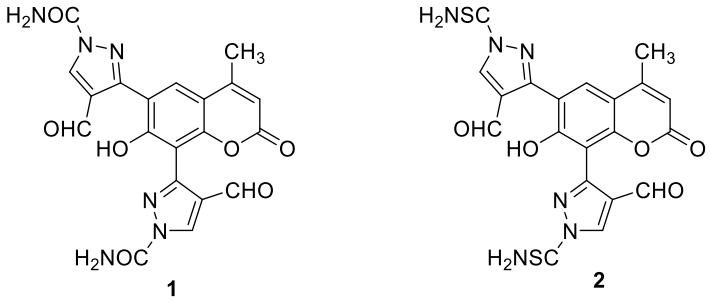


Figure 2.4 Antioxidants

Several novel pyrazolyl alcohols, pyrazolyl azides, and pyrazolyl triazoles were synthesized by Cherupally Dayakar et al., and tested for bioactivities such as antibacterial and anti-inflammatory activity. Against M. luteus bacteria, compound **3** demonstrated antibacterial action with a MIC value of 3.9. In vitro anti-inflammatory activity data revealed that compound **4** is the most efficient against IL-6 (Interleukin 6) (**Figure 2.5 a**) (Dayakar et al. 2017). Similarly, in 2018, the antibacterial and antifungal activity of three new quinoline derivatives having a pyrazole moiety has been investigated by Mohamed F. El Shehry and co-workers (**Figure 2.5 b**) (El Shehry et al. 2018).

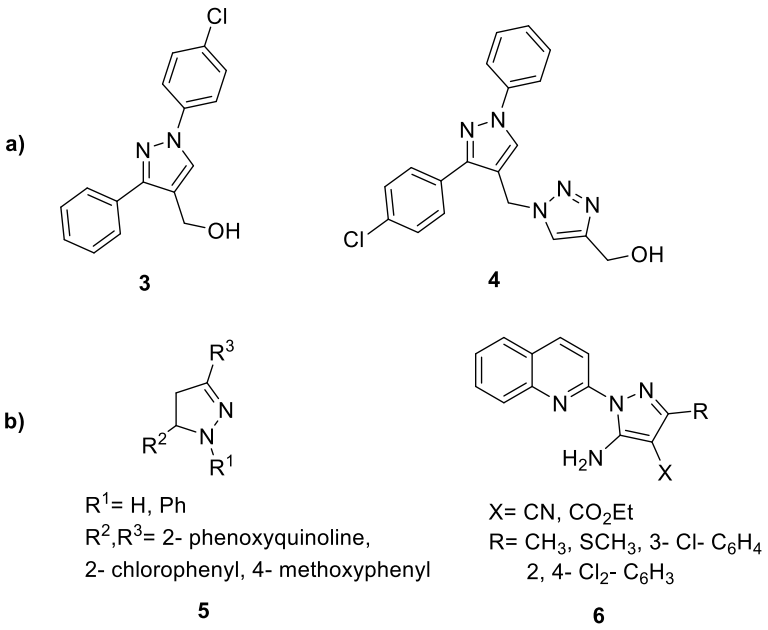


Figure 2.5 a) Compounds showing antibacterial and anti-inflammatory activity. b) Compounds showing antibacterial and antifungal activity

Nagabhushana Nayak et al., in 2017, designed, synthesized, and characterized new series of 8-trifluoromethyl quinoline substituted pyrazole-3-carboxamides derived from

various primary and secondary amines. They were tested for antitubercular activity against MTB. With a MIC of 3.13g/ mL, two compounds, **7** and **8**, emerged as the most active molecules in the series (**Figure 2.6 a**) (Nayak et al. 2017). As anticancer medicines, a series of new indole derivatives connected to the pyrazole moiety were proposed and generated by Ashraf S. Hassan et al. (**Figure 2.6 b**) (Hassan et al. 2021).

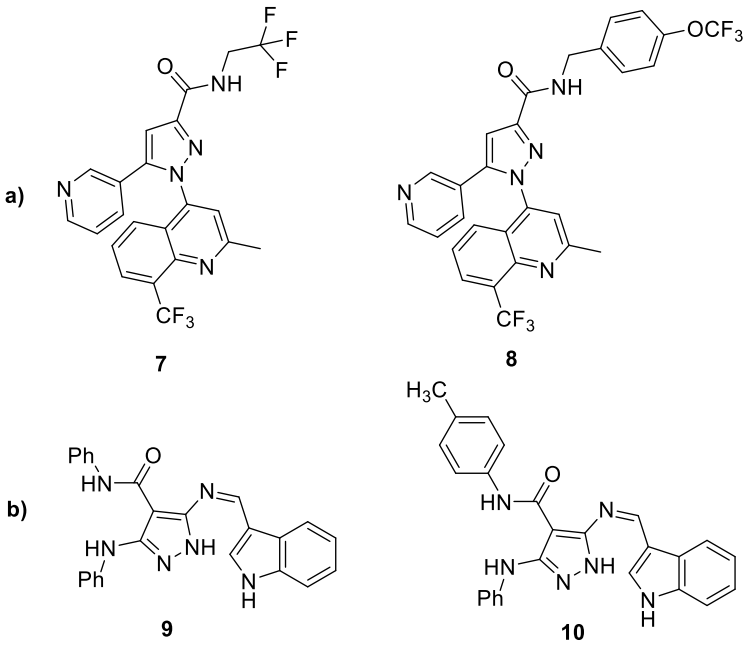


Figure 2.6 a) Compounds showing antitubercular activities. b) Compounds used as anticancer medicines

A methodology was developed to synthesize substituted pyrazole derivatives using hydrazines and 1, 3-diketones in a cyclization reaction by Fikret Turkan and co-workers. The synthesized molecules were found to be good candidate drugs for treating diseases like mountain sickness, epilepsy, glaucoma, gastric and duodenal ulcers, neurological disorders, osteoporosis, and Alzheimer's disease (**Figure 2.7a**) (Turkan et al. 2018). Yunyun Wang et al. designed, produced, and tested a series of new pyrazole ring-containing isolongifolanone derivatives for anti-proliferative properties in three cancer cell lines. Compound **13** was the most effective anti-proliferative agent on MCF-7 cancer cells, causing intracellular ROS production and mitochondrial depolarization (Wang et al. 2021).

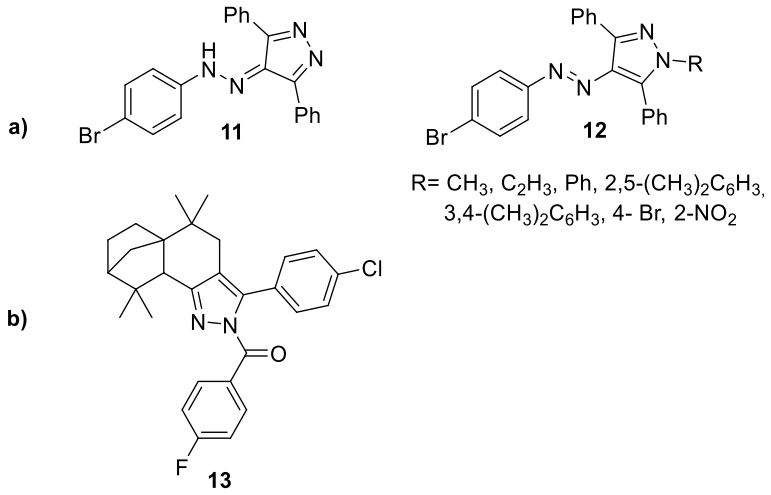


Figure 2.7 a) Compounds used for Alzheimer's disease treatment. b) anti-proliferative agent on MCF-7 cancer cells

Colorimetric and fluorescent probes based on tiny organic compounds have become vital tools in modern biology. Compared to other commonly used scaffolds, pyrazole derivatives have various unique photophysical features and vast synthetic diversity. Pyrazole does not have any fluorescent properties on its own. However, the photophysical properties of appropriately modified pyrazoles have been investigated, yielding surprising results, such as significant fluorescence quantum yields, considerable solvatochromic behavior, high Stokes shift, nonlinear optical properties, and so on.

Rangasamy Manjunath and co-workers developed and produced pyrene attached pyrazoline compounds. The colorimetric and fluorescent response of Al^{3+} ion may be easily observed with the naked eye, making it a useful Al^{3+} ion chemosensor. Fluorescence imaging investigations of Al^{3+} ions in live cells also illustrate their use in biological systems (**Figure 2.8a**) (Rangasamy and Palaninathan 2018). In 2020, a new pyrazole containing imidazole derivative was effectively produced and characterized using various methods by Jeya Shree Ganesan et al. With the addition of Al^{3+}/Fe^{3+} ions in an acetonitrile-water combination, sensor **16** exhibits a highly selective and sensitive fluorescence response (**Figure 2.8b**) (Ganesan et al. 2020).

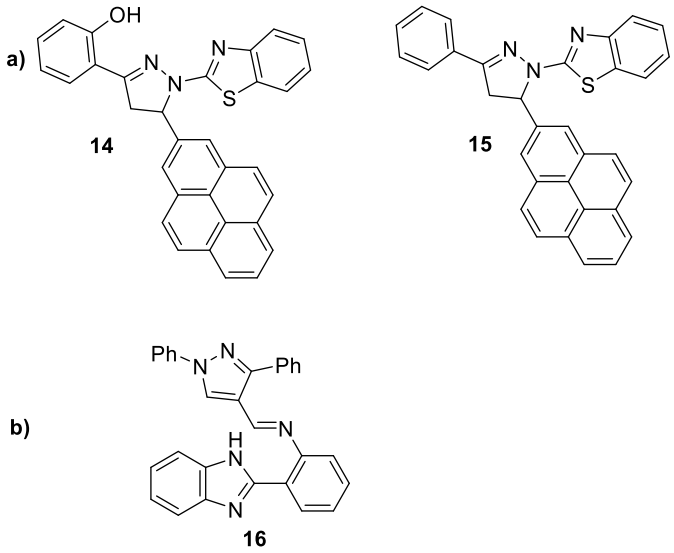


Figure 2.8 Molecules showing fluorescence response towards Al^{3+}

As multifunctional materials for organic light-emitting diodes, E. Arbačiauskiene and co-workers developed diethylene derivatives with carbazolyl and pyrazolyl moieties (**Figure 2.9)**. A similar molecule was produced and examined with different cyano groups added to the vinylene bonds. Ionization potential experiments revealed that adding cyano groups to vinylene links raises the Ip from 5.35 eV to 5.50 eV, which, when combined with PL data, results in a 0.40 eV increase in electron affinity for carbazolyl–pyrazolyl substituted diethylenes (Arbačiauskiene et al. 2010).

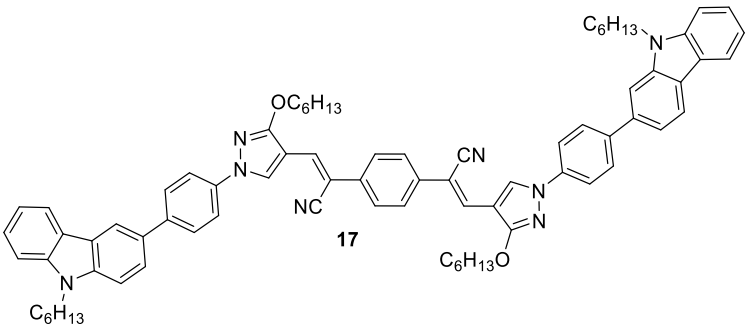


Figure 2.9 Pyrazole based compound used in OLED applications

Shambhu Kandel et al. in 2019 reported a group of compounds based on 1,3,5-triethyl benzene that can be modified to fluorescent probe applications. All the synthesized compounds are faintly fluorescent in THF. Still, when a poor solvent (water) is added, their fluorescence intensity rises, producing nano-aggregation, as evidenced by changes in UV-vis and emission spectra, as well as light scattering methods. The nano-aggregates have time-dependent emission properties and might be used as nitroaromatic

chemical sensors. The light-induced electron transfer from the tris pyrazole to the quencher is ascribed to the preferential detection of picric acid over other nitroaromatic chemicals, as verified by TD-DFT calculations (Kandel et al. 2019).

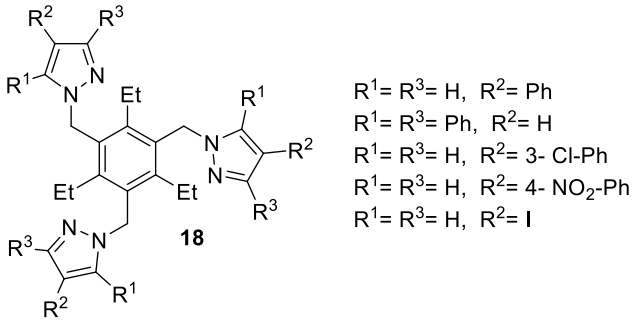


Figure 2.10 Fluorescent probes based on pyrazole

Kailasam Saravana Mani and co-workers developed and synthesized a highly sensitive probe 3-(7-(Diethylamino)-2-oxo-2H-chromen-3-yl)- 1-(4-phenylthiazol-2-yl)-1H-pyrazol-5(4H)-one from methyl 3-(7-(diethylamino)- 2-oxo-2H-chromen-3-yl)-3 oxopropanoate and 2-hydrazino- 4-phenyl thiazole for the detection of Cr^{3+} ions. Absorption and steady-state fluorescence spectrum measurements were used to study the interactions of receptor compounds with different ions. The findings show that the complexation of Cr^{3+} ions with the probe produces 1:1 stoichiometry, resulting in a rapid colour change from fluorescent bright green to colourless. Theoretical calculations confirm the photophysical changes, such as absorbance and emission spectrum alterations (Mani et al. 2018).

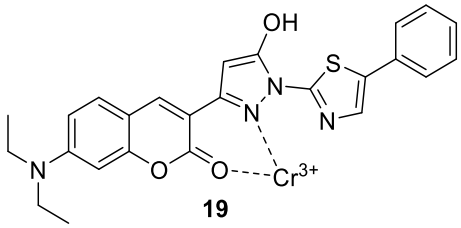


Figure 2.11 Cr^{3+} detector based on pyrazole

Pyrazoles have become appealing synthetic targets because of the vast spectrum of biological activity associated with them. For the production of substituted pyrazoles, various techniques have been devised. The reaction of α,β-unsaturated aldehydes with hydrazine (Desai et al. 2011), the condensation of 1,3-diketones with hydrazines (Fustero et al. 2008), the reaction of malononitrile with hydrazines (Taylor and Hartke

2002), and the [3+2]- cycloaddition reactions of 1,3-dipoles with alkynes are some the well-explored synthetic routes for the pyrazole preparation.

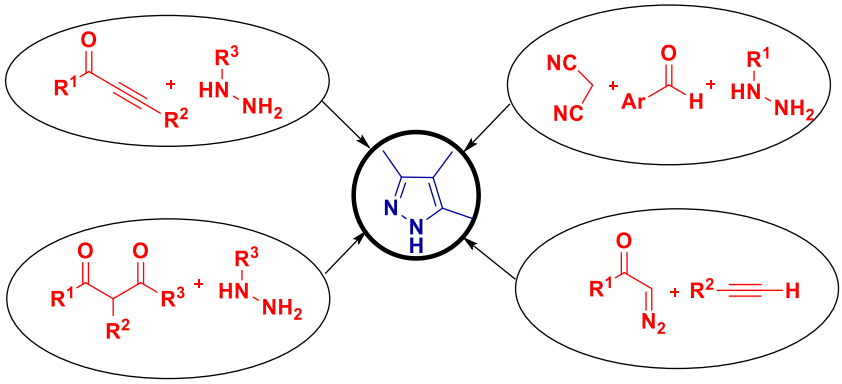


Figure 2.12 General methods for the synthesis of pyrazoles

However, these procedures also suffer from severe flaws, such as high temperature, prolonged reaction time, sensitive substrates, and lack of selectivity. As the demand for atom economic, environment-friendly, and cost-effective synthetic routes with excellent selectivity is relatively high, many previously reported strategies to synthesize pyrazole fail to meet such demands. Synthetic chemists constantly refine the protocols and develop new methods to convert pyrazole synthesis to an ideal route. Alkynes and nitrogen sources have been used to make significant progress in the synthesis of pyrazoles in recent years (Neto and Zeni 2020), as shown in **Table 2.1**.

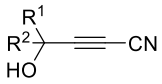
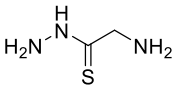
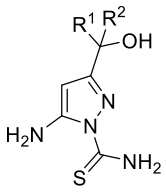
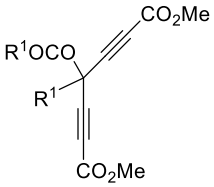
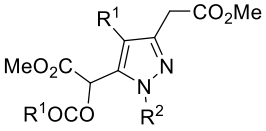
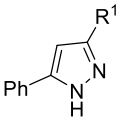
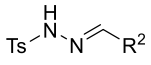
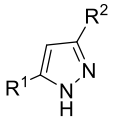
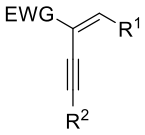
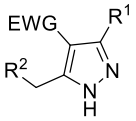
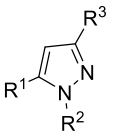
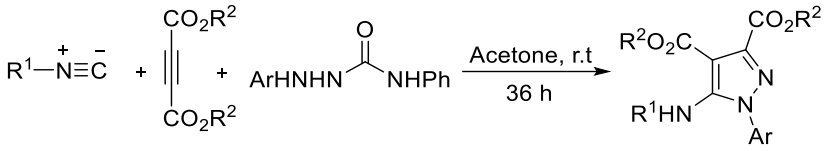
Entry	Alkynes	Reagents	Pyrazoles
1		 Ethanol, RT	
2		R^2NHNH_2, tBuOH MW (100W, 100^0C)	
3		 1. $TsNHNH_2$, Toluene 50^0C, 1.5 h 2. NaOEt, r.t, 15 min	
4		 TfOH, DCE, Reflux	
5		H_2NNHR K_2CO_3 (20 mol%) DMA, air, r.t, -40^0C	
6		 t- BuOK, 18- crown-6 Pyridine, 0^0C	

Table 2.1 various nitrogen compounds used for the amination of alkynes to generate pyrazoles

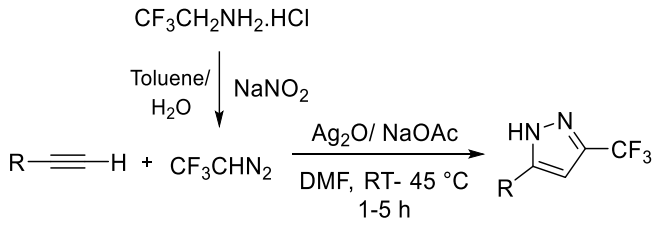
Mehdi Adib and co-workers developed a three-component reaction involving isocyanides, hydrazinecarboxamides, and dialkyl acetylenedicarboxylates, which yields 5-alkylamino-1H-pyrazoles in one pot. The title compounds were obtained in

good yields by trapping the reactive 1:1 zwitterionic intermediate generated by adding isocyanides to dialkyl acetylenedicarboxylates with hydrazinecarboxamides. The reaction proceeds at room temperature without any pre-functionalization of the starting substrates (Adib et al. 2008).



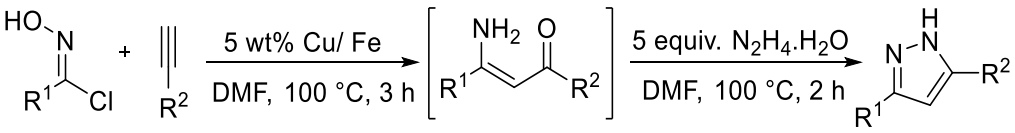
Scheme 2.1

Synthesis of 3-trifluoromethylpyrazoles was carried out by a cycloaddition reaction of terminal alkynes with CF_3CHN_2. The optimal reaction conditions for this silver-mediated cycloaddition reaction were found to be Ag_2O and NaOAc in DMF at 45 °C. After the reaction, the recovery of silver species could significantly reduce the cost and waste, allowing for a wide range of uses. The reaction is highly regioselective, and the compounds have a wide range of uses in synthetic chemistry (Li et al. 2013).



Scheme 2.2

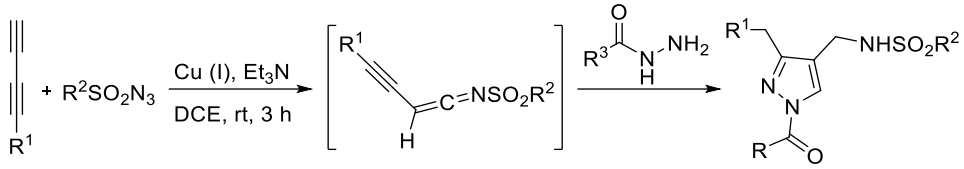
A metal-catalyzed sequential one-pot synthesis of disubstituted pyrazoles was reported by Kovacs et al. in 2014. By reductive ring opening of isoxazole intermediates, hydroximoyl chlorides react with acetylenes in the presence of a copper on iron bimetallic system to produce β-aminoenones. The β-aminoenones formed then react with hydrazine at elevated temperatures to yield the pyrazole derivative (Kovacs and Novak 2014).



Scheme 2.3

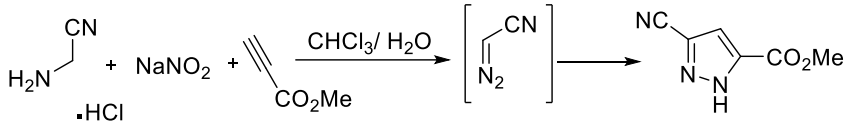
Copper-catalyzed three-component reactions of butadiynes, sulfonylazides, and hydrazides or imidamides yielded 3-aminopyrazoles and 4-iminopyrimidines. As a 1,

3-dielectrophilic equivalent, β-alkynyl-N-sulfonyl ketenimine intermediate was used, which yielded 3-aminopyrazoles and 4-iminopyrimidines in moderate to good yields with high regioselectivity. In the presence of CuI, butadiyne interacts with sulfonyl azide through a copper alkyne-azide cycloaddition (CuAAC)/ intramolecular rearrangement to generate a ketemine that reacts with hydrazides or imidamides to lead to the final product (Xing et al. 2014).



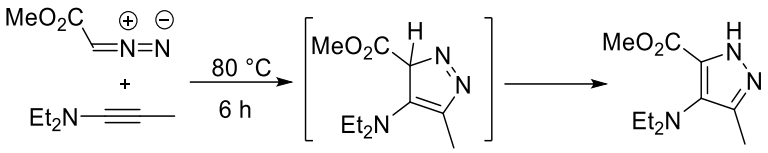
Scheme 2.4

A feasible process for the in situ production of explosive diazoacetonitrile, and its further transformation into cyano substituted pyrazoles were carried out by Pavel K. Mykhailiuk et al. Terminal alkynes were used as the counterpart for the cycloaddition of diazoacetonitrile. However, sterically hindered alkynes required more extended reaction durations but still produced reasonable yields of the desired products. Alkynes that were less active or unactivated did not react. The technique is relatively straightforward, and the product is formed without an inert environment or catalysts. The presence of electron-withdrawing groups on the alkyne speeds up the process, while the presence of electron-donating groups slows it down (Mykhailiuk 2015).



Scheme 2.5

Martin Breugst et al., in 2018, explored the 1, 3-dipolar cycloadditions of diazomethane/diazoethane with methyl-3-(diethylamino)propiolate both experimentally and computationally using density functional theory. The good regioselectivity of these (3 + 2) cycloadditions, as well as related alkyne-diazomethane reactions, has been demonstrated experimentally. The only regioisomer obtained from the trials was methyl-3-(diethylamino)-pyrazole-4-carboxylates. Independent synthesis and decarboxylation to 3-(diethylamino)pyrazoles ensured the formation of these cycloadducts (Breugst et al. 2018).



Scheme 2.6

2.3 IMPORTANCE OF HYDRAZONE AS A SUBSTRATE

Aldehyde hydrazones, a three-atom synthon, have been extensively investigated and employed in organic synthesis, especially in the construction of various heterocycle scaffolds. They can be readily obtained by condensation of carbonyl compounds (aldehydes or ketones) with hydrazines (Xiaoyan Xu et al. 2018). Hydrazone chemistry has received much attention because of its role in the evolution of organic synthesis. Hydrazone derivatives contain a wide range of biological properties and have been used as medications for a long time (Xu et al. 2018). Hydrazones are made in the lab by reacting substituted hydrazines or hydrazides with aldehydes and ketones in organic solvents such as alcoholic solvents, tetrahydrofuran, and occasionally glacial acetic acid or ethanol-glacial acetic acid. Hydrazones can also be made by combining aryldiazonium salts with active hydrogen-containing molecules(Rollas and Küçükgüzel 2007). In hydrazone, the C-atom is both electrophilic and nucleophilic, and both N-atoms are nucleophilic; however, the amine nitrogen is more nucleophilic (Rahmat Ali et al. 2012).

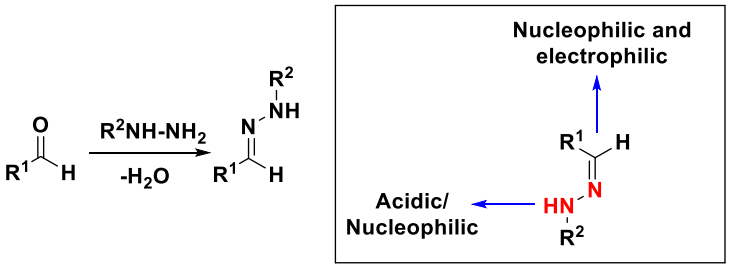


Figure 2.13 General synthesis and structure of hydrazone

Hydrazones can be thought of as 2-azaenamines from the structural standpoint, and as such, they act as ambident nucleophiles that react with electrophiles at the amine sp^3 nitrogen or the azomethine carbon via the n-π conjugation (de Gracia Retamosa et al. 2016). Because of the intrinsic polarization of the C=N bond, the electron density at the β -carbon atom of hydrazone is lower than that of enamines. The high electronegativity of the nitrogen atom in the imino C=N moiety causes this inherent polarization.

Nonetheless, the nucleophilicity of the carbon atom in the hydrazone is ensured by the conjugation of the amino nitrogen lone pair with the C=N link, just as it is in enamine. As a result, just as an electrophilic substitution at the β-carbon atom of enamine, electrophilic substitution at the β -carbon atom of hydrazone is possible. The C-H bond of aldehyde hydrazones has a reduced acidity due to the imine nitrogen atom. Thus, aldehyde hydrazones are neutral acyl anion equivalents that can be used in various applications, including Aza- Michael addition reactions(Yuan et al. 2010).

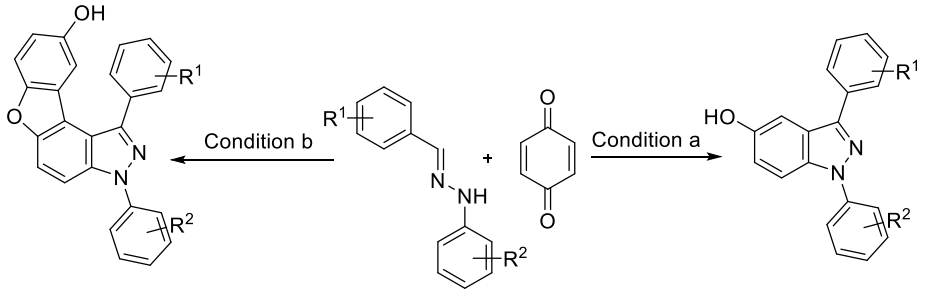
The literature shows that pyrazole is a potential scaffold often linked with potential bioactive properties and material chemistry applications. Therefore, the development of new and modified methods for the synthesis of pyrazoles is an area of active research in synthetic chemistry. Methods already reported in the literature include the condensation of 1, 3-dicarbonyl compounds with hydrazines, 1, 3-dipolar cycloaddition reaction of dipolarophiles with appropriate dipoles, and many more. Knorr reaction involving condensation of substituted hydrazines with 1, 3-dicarbonyl compounds or their derivatives lack regioselectivity. The 1, 3-dipolar cycloaddition of diazoalkanes or nitrilimines with olefins or alkynes is the most widely used protocol to synthesize pyrazole though the reactivity and stability of various 1, 3-dipoles still pose some challenges. Many other reaction pathways are also present, which requires pre-functionalized substrates, vigorous conditions, sensitive reagents, and prolonged time. Hence, efficient and simple routes towards the development of pyrazole are always noteworthy as the scaffold is of much importance in drug development and material chemistry.

Hydrazones, derived from the reaction of hydrazine with ketones or aldehydes, have been used to synthesize functionalized heterocycles. They are known to react with activated alkenes and alkynes to afford pyrazole and pyrazolidines. The scope of this reaction is broad and offers excellent functional group tolerance, and can be applied to a wide range of substrates to synthesize the pyrazole library. Because of this, it has been planned to design and develop new and more efficient synthetic routes to pyrazoles with high diversity, which can be tuned further for specific applications.

2.4 PRESENT WORK

2.4.1 Background to the work

We recently reported an efficient method for the synthesis of 5-hydroxyindazoles from aryl hydrazones and 1,4- benzoquinones (Janardhanan et al. 2018). Subsequently, the strategy was extended towards the synthesis of hybrid polycycles containing a fused indazole and benzofuran unit in one pot (Janardhanan et al. 2019).



Condition a) Hydrazone (1 equiv.), Benzoquinone (1.2 equiv.),$Pd(OAc)_2$ (5 mol%),TFA (3.5 mmol), 1,2- DCE (2 ml), N_2, 75 °C, 6 h
Condition b) Hydrazone (1 equiv.), Benzoquinone (3 equiv.),$Pd(OAc)_2$ (5 mol%),TFA (7 mmol), 1,2- DCE (2 ml), N_2, 75 °C, 6 h

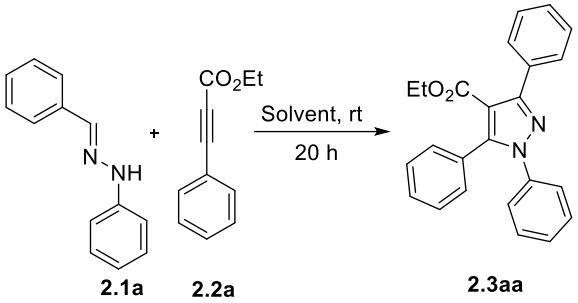
Scheme 2.7

In the light of our continued interest in the chemistry of aryl hydrazones and dipolar cycloaddition reactions, we envisioned that the annulation of aryl hydrazones across alkynes to afford pyrazole is an accessible route. Only a few reports are available in the literature in this direction. In 2011, Chaowei Ma et al. reported copper (I) catalyzed addition of hydrazone to symmetrical alkynes in the presence of an inorganic base (Ma et al. 2011). Another approach, in which $La(OTf)_3$ catalyzed the addition of salicylaldehyde hydrazones to activated alkynes at elevated temperature, was reported by Hariprasad and co-workers in 2016 (Hariprasad et al. 2016).

2.4.2 Pilot experiment

We started our investigations with the unsymmetrical alkyne, ethyl phenylpropiolate (**2.2a**), and the hydrazone 1-benzylidene-2-phenylhydrazine (**2.1a**) at room temperature under air (**Scheme 2.8**). 1-benzylidene-2-phenylhydrazine (**2.1a** 0.5 mmol, 98 mg) and ethyl phenylpropiolate (**2.2a** 0.6 mmol, 105 mg, 99.5 µl) were taken in an oven-dried Schlenk tube. To this, 2 ml of acetonitrile was added. The mixture was allowed to stir at room temperature for 20 h. We were successful to isolate 20% of ethyl 1, 3, 5-

triphenyl-1H-pyrazole-4-carboxylate (**2.3aa**). The structure of the product **2.3aa** was confirmed using FTIR, ^{1}H NMR, ^{13}C NMR, and mass spectrometry.



Scheme 2.8

An absorption band at 1704 cm^{-1} confirms the presence of the ester C=O group in the compound. The structure was further confirmed by taking the ^{1}H NMR spectra, the fifteen aromatic protons present in the compound were observed to resonate from δ= 7.70- 7.35 ppm. The quartet found at δ= 4.00 ppm correlates with the two $–OCH_2$- protons and the triplet at δ= 0.9 ppm with the three methyl protons (**Figure 2.14)**. In ^{13}C NMR spectra, the carbonyl carbon atom shows the resonance signal at δ = 163.8 ppm, and all aromatic carbon atoms within the region δ = 153.3- 112.2 ppm. The aliphatic carbon atoms of the ester group were found to resonate at δ = 60.3, 13.7 ppm (**Figure 2.15)**. The mass of the compound obtained from the HRMS was also in good agreement with the proposed pyrazole structure. HRMS (ESI) calculated for $C_{24}H_{21}N_2O_2$ $[M+H]^+$ is 369.1598, and the obtained value is 369.1611 (**Figure 2.16)**.

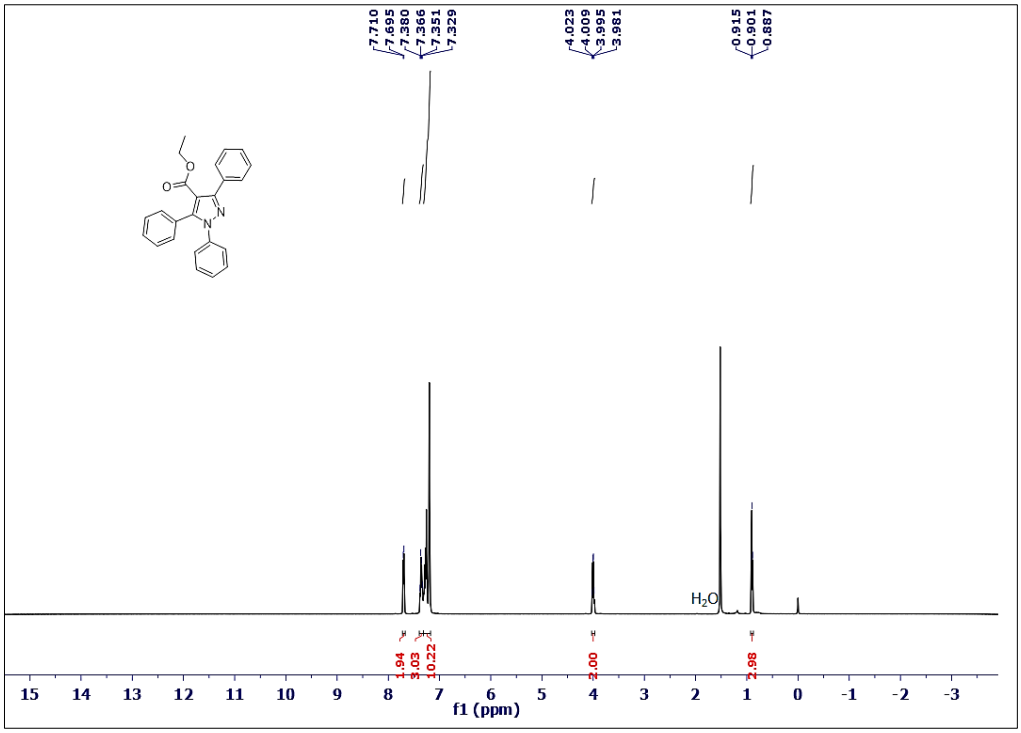


Figure 2.14 ^{1}H NMR spectrum of **2.3aa**

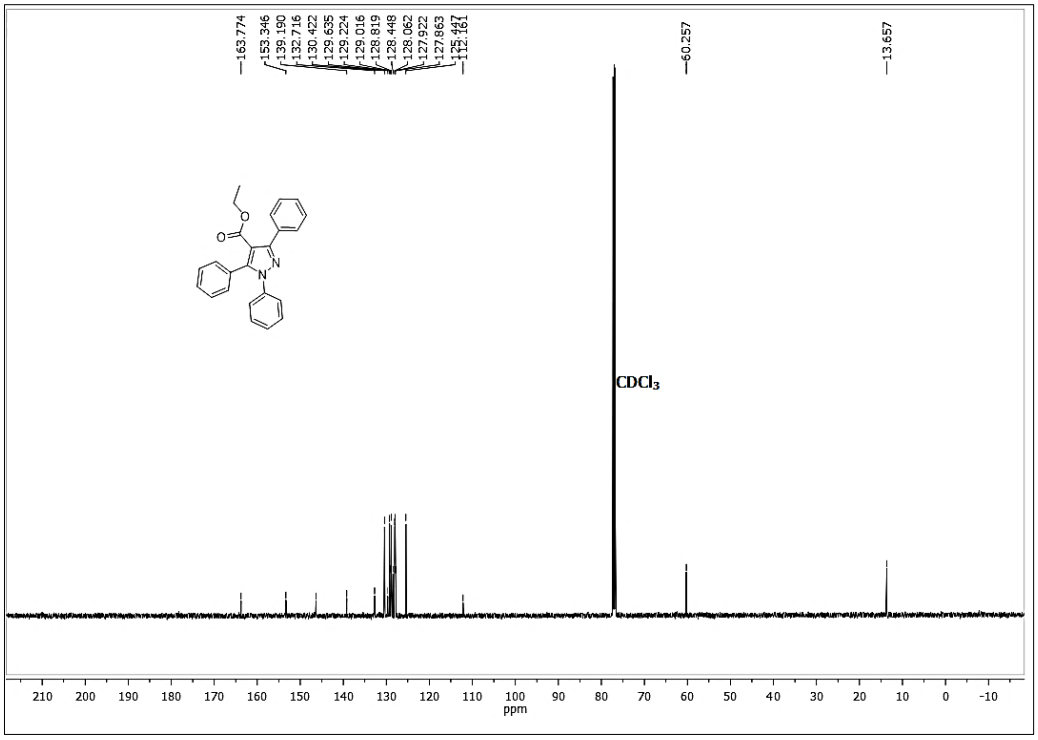


Figure 2.15 ^{13}C NMR spectrum of **2.3aa**

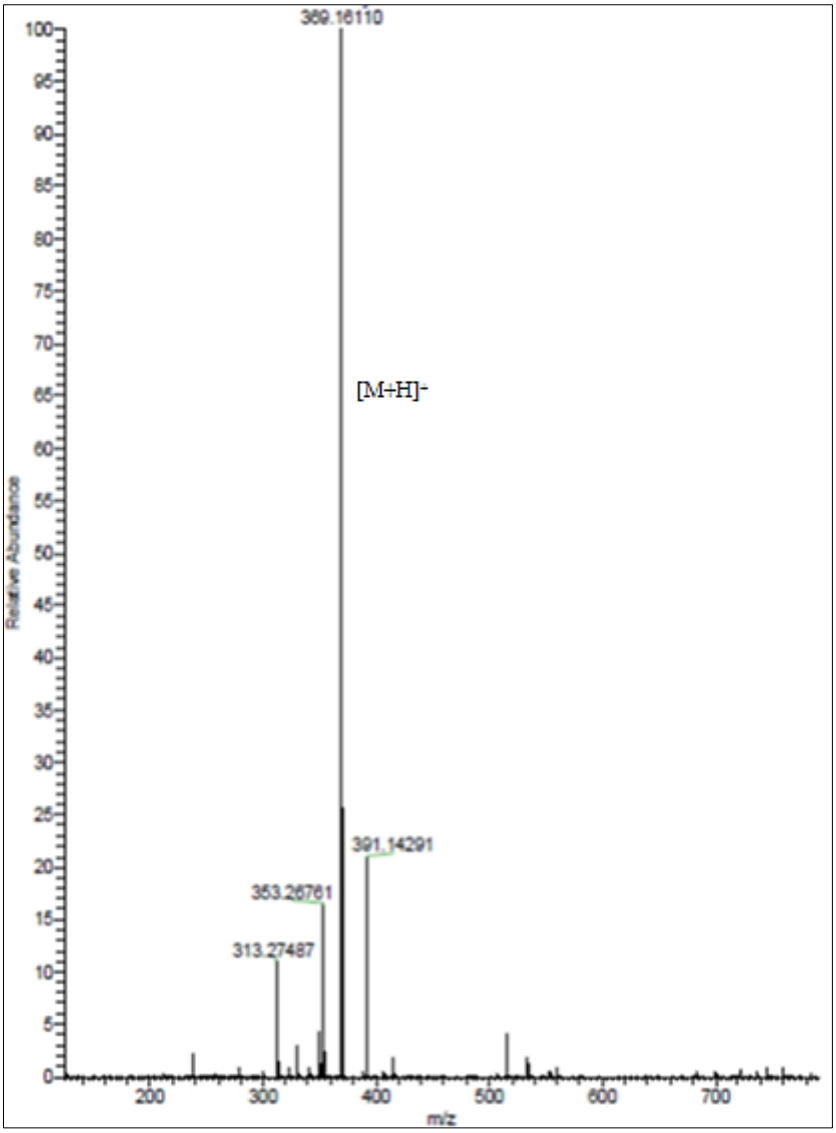


Figure 2.16 HRMS spectrum o**f 2.3aa**

2.4.3 Optimization of the reaction conditions

The optimization studies are summarized in **Table 2.2.** The reaction failed to afford the expected pyrazole in good yield when other solvents, both protic and aprotic, were used in place of acetonitrile. Only in acetonitrile, pyrazole formation was observed with an isolated yield of just 20%. However, the expected pyrazole was isolated in moderate yield when trifluoroacetic acid (TFA) was used as an additive along with the solvent. As shown in the Table, both TFA: acetonitrile and TFA:1,2-dichloroethane (DCE) mixtures resulted in the expected pyrazole but in 32-38% yield.

Interestingly, in pure TFA (2 mL), the annulation of the aryl hydrazone across the propiolate was very effective, and the corresponding pyrazole was isolated as a white solid in 69% yield, which was later identified as the best condition for the annulation. Replacing TFA with acetic acid and pivalic acid didn't help further as the conversion was poor in acetic acid while it failed in pivalic acid. The characterization of the final product was carried out using standard spectroscopic techniques such as IR, ^{1}H NMR, ^{13}C NMR, and HRMS and was in good agreement.

Entry	Solvents [a]	Yield(%)[b]
1	Acetonitrile	20
2	DCE	Trace
3	Ethyl acetate	Trace
4	DME	Trace
5	Methanol	Nil
6	TFA+ DCE (1:3)	32
7	TFA+ Acetonitrile (1:3)	38
8	TFA	69
9	Acetic acid	Trace
10	Pivalicacid	Nil

[a] All reactions were carried out in a Schlenk tube with hydrazine (0.5 mmol), ethyl phenylpropiolate (0.6 mmol, 1.2 equiv.), and TFA (2 ml. 0.25 M) under air. [b] Isolated yield after column chromatography is reported.

Table 2.2 Optimization of reaction conditions.

2.4.4 Substrate Scope of the Reaction – Synthesis of diversely functionalized pyrazoles

With the optimized reaction conditions, the substrate scope of the reaction was examined, both for the hydrazones and the acetylenic partner. Interestingly, along with ethyl phenylpropiolate, other unsymmetrical acetylenic esters, especially the terminal ones such as ethyl propiolate and methyl propiolate readily annulated to afford the pyrazoles in moderate to good yield (Compounds **2.3ac** and **2.3ad**). The strategy was not limited to propiolates alone, as the acetylic ketone yielded the expected pyrazole in 51% yield (Compound **2.3ae**). The electronic nature of the aldehyde substituent in the hydrazone didn't directly correlate with the conversion, and moderate to good conversion was observed irrespective of the electronic nature of the substituents. All these observations have been summarized in **Table 2.3.**

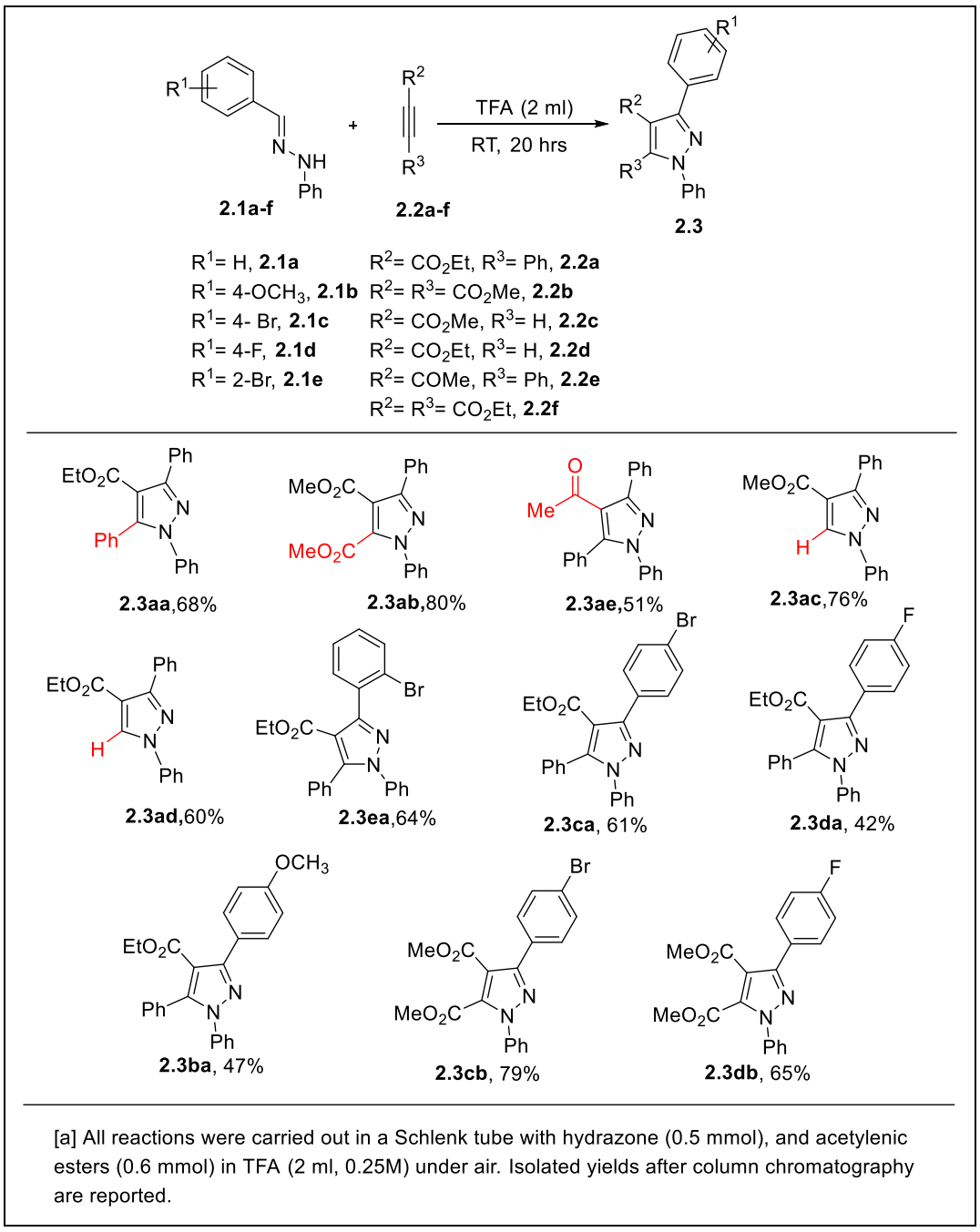


Table 2.3 Synthesized of pyrazole derivatives.

The crystal structure of one of the derivatives **2.3ea** was confirmed unambiguously by the SCXRD analysis, and the ORTEP diagram is shown in **Figure 2.17**.

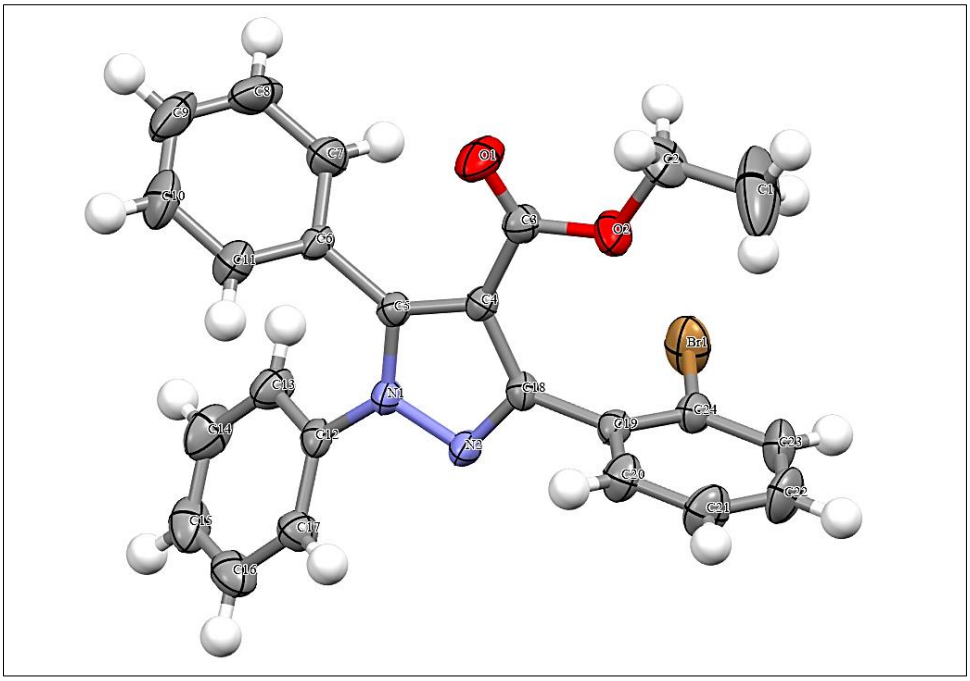
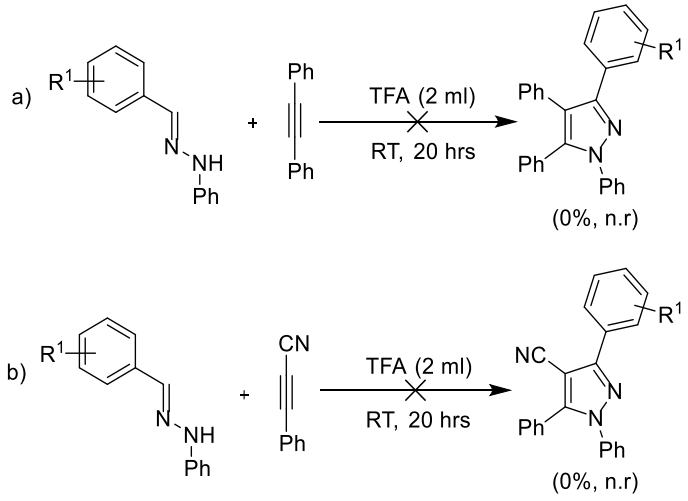
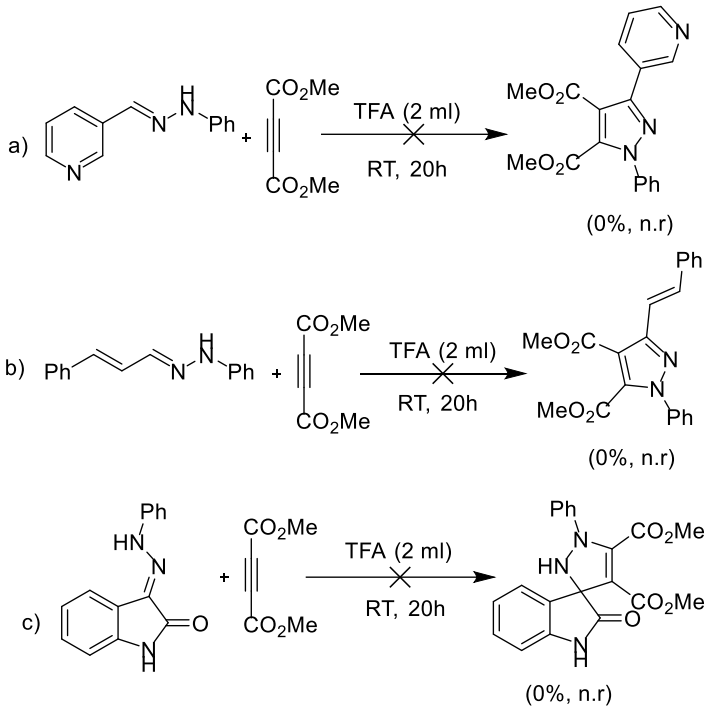


Figure 2.17 ORTEP diagram of **2.3ea**

However, 3-phenylpropiolonitrile and the symmetrical diphenyl acetylene failed to afford the product (**Scheme 2.9**). Similarly, hydrazones such as 3-((2-phenylhydrazono)methyl)pyridine, 1-phenyl-2-((E)-3-phenylallylidene)hydrazine, and 3-(2-phenylhydrazono)indolin-2-one did not react with acetylenic esters **(Scheme 2.10**).



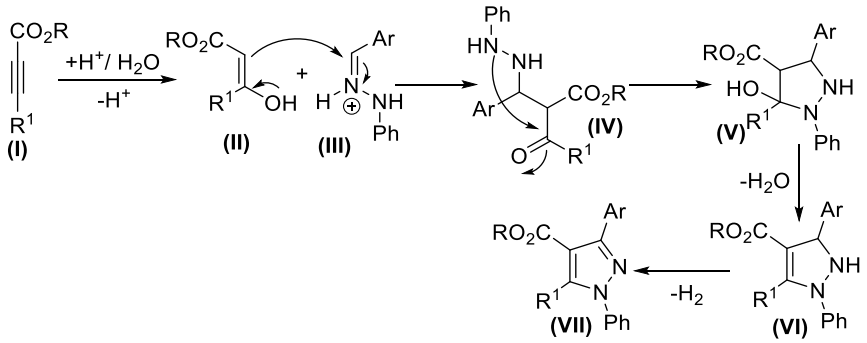
Scheme 2.9



Scheme 2.10

2.4.5 Plausible Mechanism

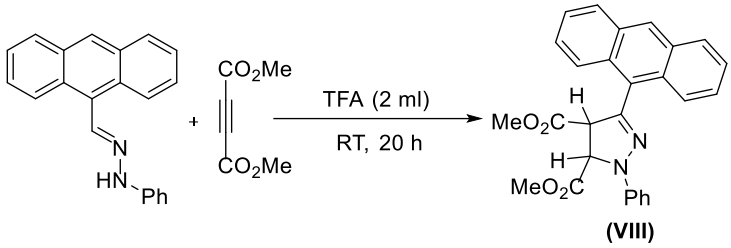
Based on our observations, a plausible mechanism for the reaction is depicted in **scheme 2.11**. The reaction starts with the hydration of the acetylenic ester to a β-ketoester (**II**), which then adds to the protonated hydrazone to afford intermediate (**IV**). Intramolecular cyclization followed by dehydration and aerobic aromatization yields the pyrazole derivative (**VII**).



Scheme 2.11

Interestingly, we could isolate the intermediate dihydro pyrazole (**VIII**) as the only final product when 9-anthraldehyde hydrazone was subjected to annulation, and the expected final pyrazole was not observed (**Scheme 2.12**). Spectral data affirmed that the isolated

compound is of type (**VIII)** and not (**VII)**, possibly formed via a protonation/ deprotonation route.



Scheme 2.12

The structure of the intermediate compound **VIII** isolated after the reaction between 1-(anthracen-9-ylmethylene)-2-phenylhydrazine and DMAD was confirmed using FT-IR, NMR, and HRMS. The stretching band of 1727 cm^{-1} corresponds to the ester $C{=}O_{str}$ confirms the presence of the acetylenic ester part in the compound. In the ^{1}H NMR spectra of the compound, the six methoxy protons resonate and appear as two sharp singlets (each corresponding to three hydrogen atoms) at δ = 3.95 ppm and δ = 3.13 ppm, respectively. The protons on the sp^3 carbon atoms in the five-membered ring mutually couple each other and appears as two doublets at δ = 5.56 ppm and δ = 4.78 ppm, with a coupling constant of J= 6 Hz (**Figure 2.18**). Also, the sp^3 carbon atoms signals at δ = 52.3 ppm and 52.6 ppm in the ^{13}C NMR spectra of the compound confirm the intermediate as dihydro pyrazole (**Figure 2.19**). Finally, the structure was confirmed from HRMS analysis, HRMS (ESI) calculated for $C_{27}H_{23}N_2O_4$ $[M+H]^+$ is 439.1652, and the value found is 439.1666 (**Figure 2.20**).

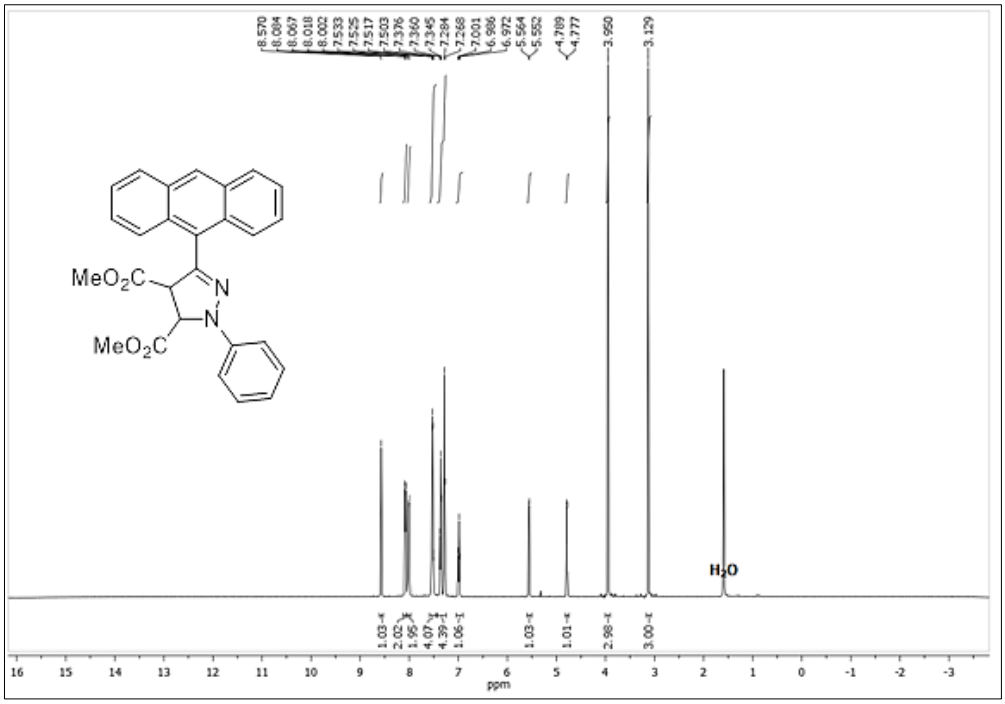


Figure 2.18 ^{1}H NMR spectrum of dihydropyrazole derivative **VIII**

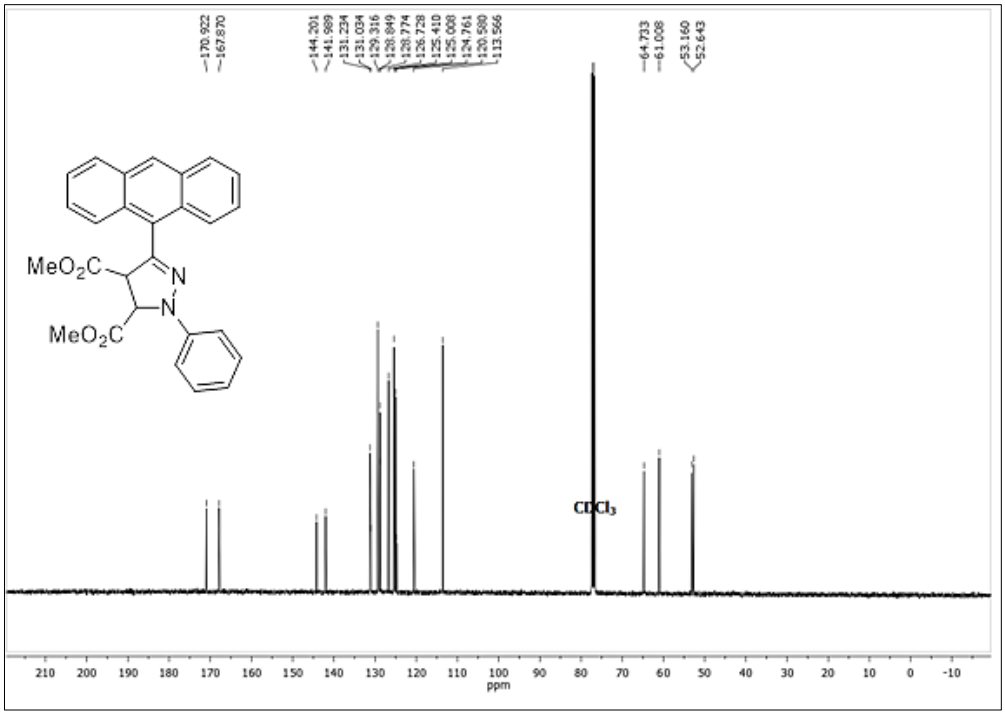


Figure 2.19 ^{13}C NMR spectrum of dihydropyrazole derivative **VIII**

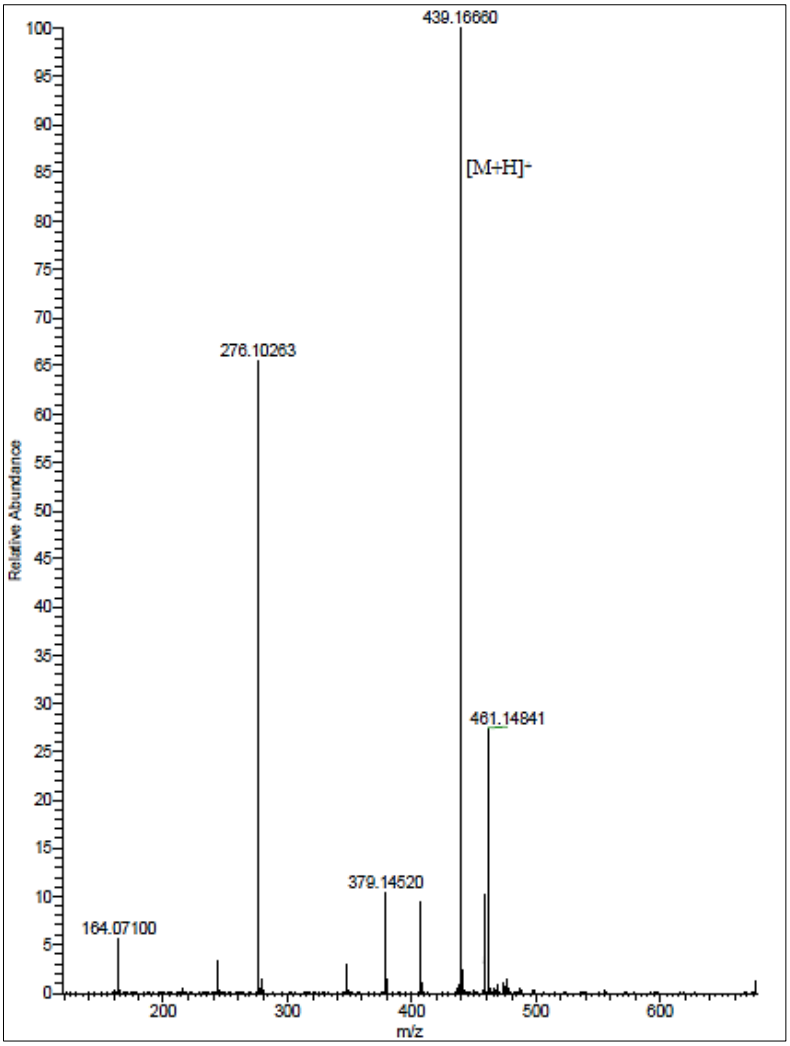


Figure 2.20 HRMS spectrum of dihydro pyrazole derivative **VIII**

2.5 CONCLUSIONS

- ✓ An efficient, one-pot synthetic route to prepare diversely substituted pyrazoles has been identified in a metal-free condition at room temperature.
- ✓ N- aryl hydrazones effectively annulated across symmetrical acetylenic ester dimethyl acetylenedicarboxylate (DMAD) to generate pyrazoles (**2.3cb** & **2.3db**).
- ✓ Unsymmetrical alkyne- ethyl phenylpropiolate (**2.2a**) and less reactive terminal alkynes- methyl propiolate (**2.2c**) and ethyl propiolate (**2.2d**) also resulted in pyrazole derivatives in moderately good yields.

- ✓ Apart from acetylenic esters, acetylenic ketone- 4-phenylbut-3-yn-2-one (**2.2e**) was found to be an effective substrate for the reaction resulting in 1-(1,3,5-triphenyl-1H-pyrazol-4-yl)ethan-1-one (**2.3ae**).
- ✓ The synthesized derivatives were exclusively characterized using FTIR, ^{1}H NMR, ^{13}C NMR, and HRMS analysis.
- ✓ The SCXRD analysis of derivative **2.3ea** confirmed the crystal structure of the compound.
- ✓ The reaction intermediate dihydropyrazole (**VIII**) was isolated during the reaction of 1-(anthracen-9-ylmethylene)-2-phenylhydrazine with DMAD, and the structure was confirmed by the spectral techniques.
- ✓ Abundant, stable, and cheap starting materials, broad substrate scope, metal-free approach, robust and moderate reaction conditions are the merits of this strategy.

2.6 EXPERIMENTAL SECTION

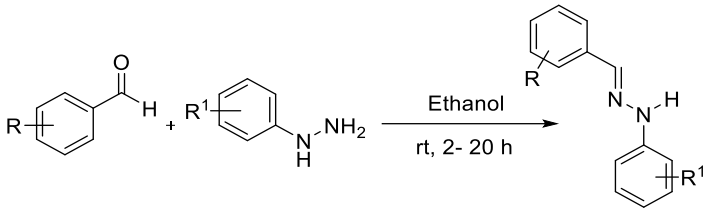
2.6.1 General Techniques used

All the reagents, chemicals, and solvents were purchased from commercial chemical suppliers and used as such without further purifications. Hydrazones were synthesized by following standard procedures. All the reactions in the optimized conditions are carried out in a schlenk tube in 2 ml solvent; the progress of the reaction was monitored by checking TLC (Loba $60F_{254}$; 0.2 mm). The spots were visualized in a UV chamber under UV light (254 and 365 nm). All the synthesized compounds were subjected to column chromatography using silica gel (100-200 mesh size), and pet ether-ethyl acetate eluent.

Melting points of all the solid samples were determined using the Stuart melting point apparatus. Other characterizations such as ^{1}H NMR (400 and 500 MHz) and ^{13}C NMR spectra were recorded in $CDCl_3$/ DMSO, on Bruker Ascend^{TM} 400 MHz, Bruker Avance DPX 500 MHz spectrometers with tetramethylsilane (TMS; δ= 0 ppm) as an internal standard and chemical shifts were reported in ppm relative to TMS. The resonance multiplicity is described as s (singlet), d (doublet), t (triplet), m (multiplet), dd (doublet of doublets), and q (quartet). Infrared spectra were recorded on JASCO

FTIR-4100 using ATR, and only intense peaks were reported. Electrospray ionization (ESI) high-resolution mass spectra were recorded using Thermo Scientific Exactive mass spectrometer.

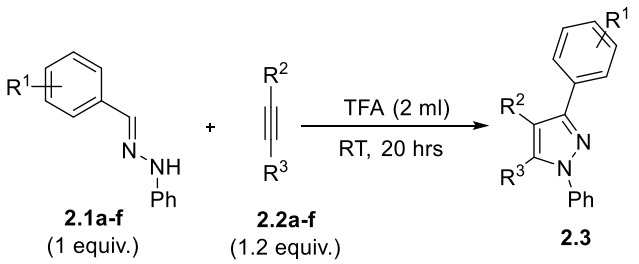
2.6.2 Synthesis of starting material- Hydrazones



Scheme 2.13

A solution of phenylhydrazine (1 equiv.) in ethanol was stirred at room temperature in a round bottom flask. Corresponding aldehyde (1 equiv.) was added to the solution (solid aldehyde was added portion-wise and liquid aldehyde dropwise) and stirred the mixture for about 2- 20 hours (depending on the electronic nature of aldehydes). TLC was checked to monitor the progress of the reaction. After the completion of the reaction, the mixture was poured into ice-cold water. The precipitate formed was filtered off, washed with ice-cold water followed by pet ether. The solid mass obtained was dissolved in dichloromethane, dried using Na_2SO_4. The solvent was evaporated under vacuum, and the product obtained was used as such for all other reactions.

2.6.3 General procedure for the synthesis of pyrazole derivatives



Scheme 2.14

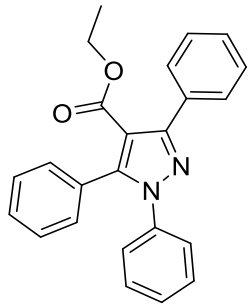
Hydrazone (0.5 mmol, 1equiv.) was taken in an oven-dried schlenk tube equipped with a magnetic stirrer. To this, alkyne (0.6 mmol, 1.2 equiv.) was added, followed by 2 ml TFA (solvent). The reaction was kept at room temperature for about 20 h with continuous monitoring by checking TLC. The reaction mixture was then washed with saturated $NaHCO_3$ solution, and the organic layer was extracted in ethyl acetate. The ethyl acetate layer was finally washed with brine solution and distilled water. Dried

over anhydrous sodium sulphate and evaporated under reduced pressure. The residue was purified by silica gel column chromatography using pet ether- ethyl acetate as eluent.

2.7 SYNTHESIS AND CHARACTERIZATION OF COMPOUNDS 2.3aa TO 2.3db.

2.7.1 Ethyl 1, 3, 5-triphenyl-1H-pyrazole-4-carboxylate (2.3aa)

Following the general procedure, the reaction between 1-benzylidene-2-phenyl hydrazine (0.5 mmol, 98 mg) with ethyl phenyl propiolate (0.6 mmol, 105 mg, 99.5 μl) yielded the desired product ethyl 1, 3, 5-triphenyl-1H-pyrazole-4-carboxylate as a white solid in 68% yield (125 mg).



Chemical Formula: $C_{24}H_{20}N_2O_2$

Melting point 140-142° C.

FT-IR (ATR): ν_{max}**=** 3050, 2984, 1704, 1590, 1489, 1449, 1295, 1246, 1138, 1088, 1023 cm^{-1}

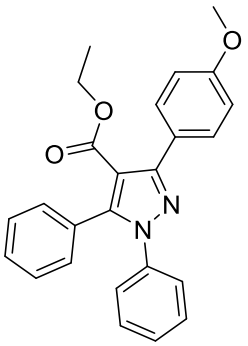
^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.70 (d, *J* = 7.5 Hz, 2H), 7.38- 7.35 (m, 3H), 7.30 –7.20 (m, 10H), 4.00 (q, *J* = 7.0 Hz, 2H), 0.90 (t, *J* = 7.0 Hz, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ = 163.8, 153.3, 146.3, 139.2, 132.7, 130.4 (2 C), 129.6, 129.2 (2 C), 129.0, 128.8 (2 C), 128.4, 128.1 (2 C), 127.9 (2 C), 127.8, 125.4 (2 C), 112.2, 60.3, 13.7 ppm

HRMS (ESI) calcd for $C_{24}H_{21}N_2O_2$ $[M+H]^+$ 369.1598 found 369.1611.

2.7.2 Ethyl-3-(4-methoxyphenyl)-1, 5-diphenyl-1*H*-pyrazole-4-carboxylate (2.3ba)

Following the general procedure, the reaction between 1-(4-methoxybenzylidene)-2-phenylhydrazine (0.5 mmol, 113 mg) with ethyl phenyl propiolate (0.6 mmol, 105 mg, 99.5 μl) yielded the desired product ethyl 3-(4-methoxyphenyl)-1,5-diphenyl-1*H*-pyrazole-4-carboxylate as a white solid in 47% yield (93.5 mg).



Chemical Formula: $C_{25}H_{22}N_2O_3$

Melting point 110-112°C.

FT-IR (ATR): ν_{max}**=** 3048, 2921, 2853, 1706, 1602, 1488, 1447, 1365, 1291, 1241, 1169, 1088, 1019 cm^{-1}

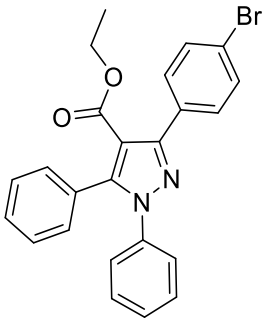
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.67(d, *J* = 7.6 Hz, 2H), 7.30 –7.19 (m, 10H), 6.90 (d, *J* = 7.6 Hz, 2H), 4.00 (q, *J* = 7.2 Hz, 2H), 3.8 (s, 3H), 0.91 (t, *J* = 7.2Hz, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ= 163.9, 159.9, 153.1, 146.3, 139.2, 130.5 (2 C), 130.4 (2 C), 129.8, 128.9, 128.8 (2 C), 128.0 (2 C), 127.8, 125.4 (2 C), 125.2, 113.4 (2 C), 111.9, 60.2, 55.3, 13.7 ppm

HRMS (ESI) calcd for $C_{25}H_{23}N_2O_3$ $[M+H]^+$ 399.1703 found 399.1703.

2.7.3 Ethyl-3-(4-bromophenyl)-1,5-diphenyl-1*H*-pyrazole-4-carboxylate (2.3ca)

Following the general procedure, the reaction between 1-(4-bromobenzylidene)-2-phenylhydrazine(0.5 mmol, 137 mg) with ethyl phenyl propiolate (0.6 mmol, 105 mg, 99.5 μl) yielded the desired product ethyl 3-(4-bromophenyl)-1,5-diphenyl-1*H*-pyrazole-4-carboxylate as a white solid in 61% yield (136.6 mg).



Chemical Formula: $C_{24}H_{19}BrN_2O_2$

Melting point 128-130° C.

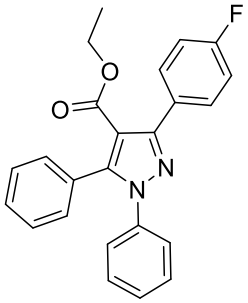
FT-IR (ATR): ν_{max}**=** 3047, 2967, 2355, 1700, 1588, 1481, 1441, 1366, 1304, 1142, 1078, 1005 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ= 7.61 (d, *J* = 7.6 Hz, 2H), 7.49(d, *J* = 7.6 Hz, 2H), 7.32 – 7.16 (m, 10H), 4.00 (q, *J* = 7.2 Hz, 2H), 0.91 (t, *J* = 7.2 Hz, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ= 163.6, 152.2, 146.6, 139.1, 131.7, 131.1 (2 C), 130.9 (2 C), 130.4 (2 C), 129.5, 129.1, 128.9 (2 C), 128.0 (2 C), 127.9, 125.4 (2 C), 122.8, 112.1, 60.3, 13.7 ppm. **HRMS (ESI)** calcd for $C_{24}H_{20}BrN_2O_2$ $[M+H]^+$ 447.0703 found 447.0725.

2.7.4 Ethyl-3-(4-fluorophenyl)-1,5-diphenyl-1*H*-pyrazole-4-carboxylate (2.3da)

Following the general procedure, the reaction between 1-(4-fluorobenzylidene)-2-phenylhydrazine (0.5 mmol, 107 mg) with ethyl phenyl propiolate (0.6 mmol, 105 mg, 99.5 μl) yielded the desired product ethyl 3-(4-fluorophenyl)-1,5-diphenyl-1*H*-pyrazole-4-carboxylate as a white solid in 42% yield (80.6 mg).



Chemical Formula: $C_{24}H_{19}FN_2O_2$

Melting point 126-128°C.

FT-IR (ATR): ν_{max}= 3055, 2982, 1699, 1595, 1485, 1447, 1303, 1226, 1144, 1094, 1019 cm^{-1}

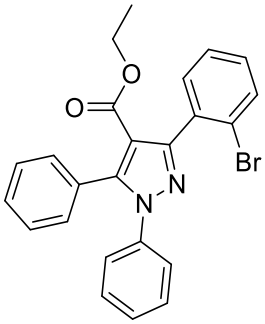
^{1}H NMR (500 MHz, $CDCl_3$) δ= 7.72- 7.69 (m, 2H), 7.32- 7.17 (m, 10H), 7.08- 7.03 (m, 2H), 3.99(q, J= 7 Hz, 2H), 0.90 (t, J= 7 Hz, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ= 168.0, 167.5 ($^1J_{CF}$= 244 Hz), 156.2, 151.5, 143.9, 136.2 ($^3J_{CF}$= 8.7 Hz, 2 C), 135.5 (2 C), 134.3, 134.26, 134.1 (2 C), 134.0 ($^4J_{CF}$= 3.0 Hz), 133.5 (2 C), 133.2, 130.9 (2 C), 120.1 ($^2J_{CF}$= 21.4 Hz, 2 C), 116.7, 65.1, 18.7 ppm

HRMS (ESI) calcd for $C_{24}H_{20}FN_2O_2$ $[M+H]^+$ 387.1503 found 387.1505.

2.7.5 Ethyl-3-(2-bromophenyl)-1, 5-diphenyl-1*H*-pyrazole-4-carboxylate (2.3ea)

Following the general procedure, the reaction between 1-(2-bromobenzylidene)-2-phenylhydrazine (0.5 mmol, 137 mg) with ethyl phenyl propiolate (0.6 mmol, 105 mg, 99.5 μl) yielded the desired product ethyl 3-(2-bromophenyl)-1,5-diphenyl-1*H*-pyrazole-4-carboxylate as a white solid in 64% yield (142 mg).



Chemical Formula: $C_{24}H_{19}BrN_2O_2$

Melting point 110-112°C.

FT-IR (ATR): ν_{max}**=** 3052, 2973, 2899, 1707, 1593, 1545, 1489, 1430, 1235, 1170, 1089, 1061, 1020 cm^{-1}

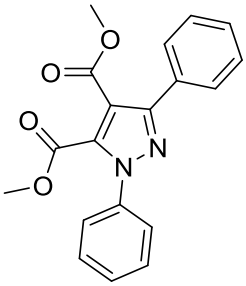
^{1}H NMR (500 MHz, $CDCl_3$) δ= 7.58(d, J= 8 Hz, 1H), 7.48 (d, J=7.5, 1H), 7.33- 7.26 (m, 6H), 7.20- 7.18 (m,6H), 3.93 (q, J= 7.5 Hz, 2H), 0.82 (t, J= 7.5, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ= 162.9, 153.0, 145.9, 139.1, 135.1, 132.3, 131.5, 130.6 (2 C), 129.8, 129.2, 128.8 (2 C), 128.0 (2 C), 127.9 (2 C), 126.9, 125.4 (2 C), 124.2, 113.1, 60.1, 13.5 ppm

HRMS (ESI) calcd for $C_{24}H_{20}BrN_2O_2$ $[M+H]^+$ 447.0703 found 449.0700 $[(M+2)+H]^+$.

2.7.6 Dimethyl 1,3-diphenyl-1*H*-pyrazole-4,5-dicarboxylate (2.3ab)

Following the general procedure, the reaction between 1-benzylidene-2-phenylhydrazine (0.5 mmol, 98 mg) with dimethylacetylene dicarboxylate (0.6 mmol, 85.2 mg, 73.45 μl) yielded the desired product Dimethyl 1,3-diphenyl-1*H*-pyrazole-4,5-dicarboxylate as a white solid in 80% yield (134 mg).



Chemical Formula: $C_{19}H_{16}N_2O_4$

Melting point 132-134°C.

FT-IR (ATR): ν_{max}**=** 3030, 2949, 1718, 1595, 1495, 1444, 1363, 1264, 1224, 1145, 1095 cm^{-1}

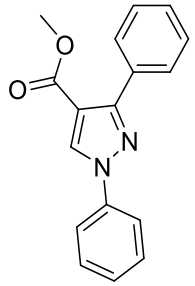
^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.77 (d, *J* = 7 Hz, 2H), 7.57 – 7.42 (m, 8H), 3.88 (s, 3H), 3.85 (s, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ = 163.4, 160.7, 152.0, 139.1, 136.9, 131.4, 129.2 (2 C), 129.1, 128.9, 128.8 (2 C), 128.2 (2 C), 124.5 (2 C), 114.2, 53.2, 52.2 ppm

HRMS (ESI) calcd for $C_{19}H_{17}N_2O_4$ $[M+H]^+$ 337.1183 found 337.1189.

2.7.7 Methyl 1,3-diphenyl-1*H*-pyrazole-4-carboxylate (2.3ac)

Following the general procedure, the reaction between 1-benzylidene-2-phenylhydrazine (0.5 mmol, 98 mg) with methyl propiolate(0.6 mmol, 50.4 mg, 53.3 µl) yielded the desired product methyl 1,3-diphenyl-1*H*-pyrazole-4-carboxylate as a white solid in 76% yield (105 mg).



Chemical Formula: $C_{17}H_{14}N_2O_2$

Melting point 88-90°C.

FT-IR (ATR): ν_{max}**=** 3122, 3048, 2945, 1695, 1597, 1526, 1435, 1360, 1267, 1228, 1185, 1127, 1054, 1012 cm^{-1}

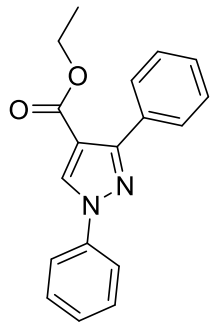
^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.44(s, 1H), 7.8 (d, J= 8 Hz, 2H), 7.71 (d, J= 8 Hz, 2H), 7.43- 7.27 (m, 6H), 3.75 (s, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ = 163.4, 154.1, 139.2, 132.3, 132.0, 129.6 (2 C), 129.3 (2 C), 128.7, 127.9 (2 C), 127.5, 119.5 (2 C), 113.3, 51.5 ppm

HRMS (ESI) calcd for $C_{17}H_{15}N_2O_2$ $[M+H]^+$ 279.1128 found 279.1141.

2.7.8 Ethyl 1,3-diphenyl-1*H*-pyrazole-4-carboxylate (2.3ad)

Following the general procedure, the reaction between 1-benzylidene-2-phenylhydrazine (0.5 mmol, 98 mg) with ethyl propiolate(0.6 mmol, 59 mg, 60.95 µl) yielded the desired product ethyl 1,3-diphenyl-1*H*-pyrazole-4-carboxylate as a white solid in 60% yield (87.6 mg).



Chemical Formula: $C_{18}H_{16}N_2O_2$

Melting point 112-114°C.

FT-IR (ATR): ν_{max}**=** 3135, 3059, 2981, 2928, 1714, 1597, 1531, 1510, 1448, 1361, 1277, 1213, 1166, 1117, 1052, 1024 cm^{-1}

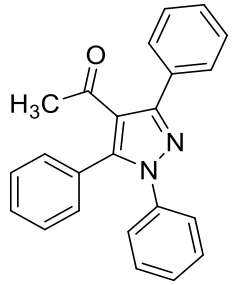
^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.44 (s, 1H), 7.79 (d, *J* = 7.2 Hz, 2H), 7.72 (d, *J* = 8 Hz, 2H), 7.44 – 7.27 (m, 6H), 4.22(q, *J* = 7.2 Hz, 2H), 1.25 (t, *J* = 7.2 Hz, 3H) ppm

^{13}C NMR (100MHz, $CDCl_3$) δ = 163.0, 154.1, 139.3, 132.3, 132.1, 129.6 (2 C), 129.4 (2 C), 128.7, 127.9 (2 C), 127.5, 119.5 (2 C), 113.8, 60.4, 14.3 ppm

HRMS (ESI) calcd for $C_{18}H_{17}N_2O_2$ $[M+H]^+$ 293.1285 found 293.1295.

2.7.9 1-(1, 3, 5-triphenyl-1*H*-pyrazol-4-yl)ethan-1-one (2.3ae)

Following the general procedure, the reaction between 1-benzylidene-2-phenylhydrazine (0.5 mmol, 98 mg) with 4-phenylbut-3-yn-2-one (0.6 mmol, 59 mg, 59.6 μl) yielded the desired product 1-(1,3,5-triphenyl-1*H*-pyrazol-4-yl)ethan-1-one as a white solid in 51% yield (86.7 mg).



Chemical Formula: $C_{23}H_{18}N_2O$

Melting point 98- 100^o C.

FT-IR (ATR): ν_{max}= 3060, 2922, 2854, 1749, 1674, 1595, 1532, 1490, 1446, 1246, 1076 cm^{-1}

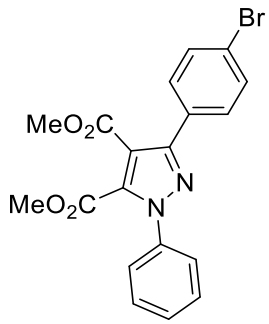
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.64-7.62 (m, 2H), 7.40- 7.17 (m, 13H), 1.99 (s, 3H) ppm

^{13}C NMR (100MHz, $CDCl_3$) δ = 196.0, 152.5, 144.8, 139.1, 132.8, 130.4 (2 C), 129.5, 129.4, 129.1 (2 C), 128.8 (2 C), 128.7, 128.5 (2 C), 128.4 (2 C), 127.9, 125.5 (2 C), 121.9, 31.3 ppm

HRMS (ESI) calcd for $C_{23}H_{19}N_2O$ $[M+H]^+$ 339.1492 found 339.1503.

2.7.10 Dimethyl 3-(4-bromophenyl)-1-phenyl-1*H*-pyrazole-4, 5-dicarboxylate (2.3cb)

Following the general procedure, the reaction between (4-bromobenzylidene)-2-phenylhydrazine (0.5 mmol, 137.5 mg) with dimethylacetylene dicarboxylate (0.6 mmol, 85.2 mg, 73.45 μl) yielded the desired product Dimethyl 3-(4-bromophenyl)-1-phenyl-1*H*-pyrazole-4,5-dicarboxylate as a white solid in 79% yield (163 mg).



Chemical Formula: $C_{19}H_{15}BrN_2O_4$

Melting point 116-118°C.

FT-IR (ATR): ν_{max}= 2948, 2925, 2859, 1727, 1594, 1532, 1496, 1447, 1365, 1300, 1261, 1230, 1157, 1110,1068 cm^{-1}

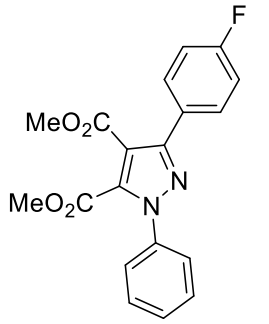
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.66- 7.64 (m, 2H), 7.57-7.45 (m, 7H), 3.86 (s, 3H), 3.83 (s, 3H) ppm

^{13}C NMR (100MHz, $CDCl_3$) δ = 163.1, 160.7, 151.1, 138.9, 137.3, 131.4 (2 C), 130.5 (2 C), 130.3, 129.3 (2 C), 129.25, 124.5 (2 C), 123.4, 113.8, 53.3, 52.2 ppm

HRMS (ESI) calcd for $C_{19}H_{15}BrN_2O_4$ $[M+H]^+$ 415.0288 found 415.0299.

2.7.11 Dimethyl 3-(4-fluorophenyl)-1-phenyl-1*H*-pyrazole-4,5-dicarboxylate (2.3db)

Following the general procedure, the reaction between (4-fluorobenzylidene)-2-phenylhydrazine (0.5 mmol, 107 mg) with dimethylacetylene dicarboxylate (0.6 mmol, 85.2 mg, 73.45 µl) yielded the desired product Dimethyl 3-(4-fluorophenyl)-1-phenyl-1*H*-pyrazole-4,5-dicarboxylate as a white solid in 65% yield (115 mg).



Chemical Formula: $C_{19}H_{15}FN_2O_4$

Melting point 102- 104° C.

FT-IR (ATR): ν_{max}= 2952, 1728, 1597, 1497, 1446, 1259, 1228, 1153, 1109, 1066 cm^{-1}

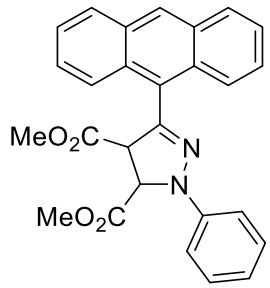
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.78- 7.73 (m, 2H), 7.55-7.44 (m, 5H), 7.15- 7.09 (m, 2H), 3.86 (s, 3H), 3.83 (s, 3H) ppm

^{13}C NMR (100MHz, $CDCl_3$) δ = 164.5, 162.0 ($^1J_{CF}$= 241.7 Hz), 160.8, 151.3, 138.9, 137.3, 130.8 ($^3J_{CF}$= 8.3 Hz, 2 C), 129.3 (2 C), 129.2, 127.5 ($^4J_{CF}$= 3.2 Hz), 124.5 (2 C), 115.2 ($^2J_{CF}$= 21.6 Hz, 2 C), 113.7, 53.2, 52.2 ppm

HRMS (ESI) calcd for $C_{19}H_{16}FN_2O_4$ $[M+H]^+$ 355.1089 found 355.1089.

2.7.12 Intermediate isolated: Dimethyl 3-(anthracen-9-yl)-1-phenyl-4,5-dihydro-1H-pyrazole-4,5-dicarboxylate VIII

Following the general procedure, the reaction between (E)-1-(anthracen-9-ylmethylene)-2-phenylhydrazine (0.5 mmol, 148 mg) with dimethylacetylene dicarboxylate (0.6 mmol, 85.2 mg, 73.45 µl) yielded the desired product Dimethyl 4-(anthracen-9-yl)-1-phenyl-2,3-dihydro-1H-pyrrole-2,3-dicarboxylate as a pale orange solid in 61% yield (134 mg).



Chemical Formula: $C_{27}H_{22}N_2O_4$

Melting point 148- 150^{o} C.

FT-IR (ATR): ν_{max}= 3016, 2950, 1727, 1588, 1492, 1439, 1378, 1332, 1249, 1200, 1123, 1008 cm^{-1}

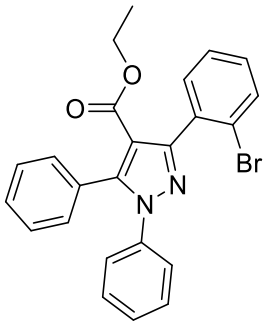
^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.57 (s, 1H), 8.08 (d, J= 8.5 Hz, 2H), 8.01 (d, J= 8 Hz, 2H), 7.53-7.50 (m, 4H), 7.38- 7.27 (m, 4H), 7.00- 6.97(m, 1H), 5.56 (d, J= 6Hz, 1H), 4.78 (d, J= 6 Hz, 1H), 3.95 (s, 3H), 3.13 (s, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.9, 167.9, 144.2, 142.0, 131.2, 131.0, 129.3, 128.8, 128.77, 126.7, 125.4, 125.0, 124.8, 120.6, 113.6, 64.7, 61.0, 53.2, 52.6 ppm

HRMS (ESI) calcd for $C_{27}H_{23}N_2O_4$ $[M+H]^+$ 439.1652 found 439.1666.

2.8 CRYSTAL DATA OF COMPOUND 2.3ea

Structure of 2.3ea:



Crystal data

Chemical formula	$C_{24}H_{19}BrN_2O_2$
M_r	447.32
Crystal system, space group	Monoclinic, $P2_1/c$
Temperature (K)	296
a, b, c (Å)	12.491 (6), 11.319 (6), 15.146 (7)
β (°)	99.618 (18)
V (Å^3)	2111.4 (17)
Z	4
Radiation type	Mo $K\alpha$
μ (mm^{-1})	1.97
Crystal size (mm)	0.16 × 0.14 × 0.13
Data collection	
Diffractometer	ApexII
Absorption correction	Multi-scan bruker, *SADABS*, 2016
T_{min}, T_{max}	0.737, 0.774
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	20606, 4836, 2996
R_{int}	0.072
$(\sin \theta/\lambda)_{max}$ (Å^{-1})	0.650
Refinement	

$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.056, 0.119, 1.05
No. of reflections	4836
No. of parameters	263
H-atom treatment	H-atom parameters constrained
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.48, −0.57

Appendix I

FTIR, ^{1}H NMR, ^{13}C NMR and HRMS spectra of some selected compounds are shown:

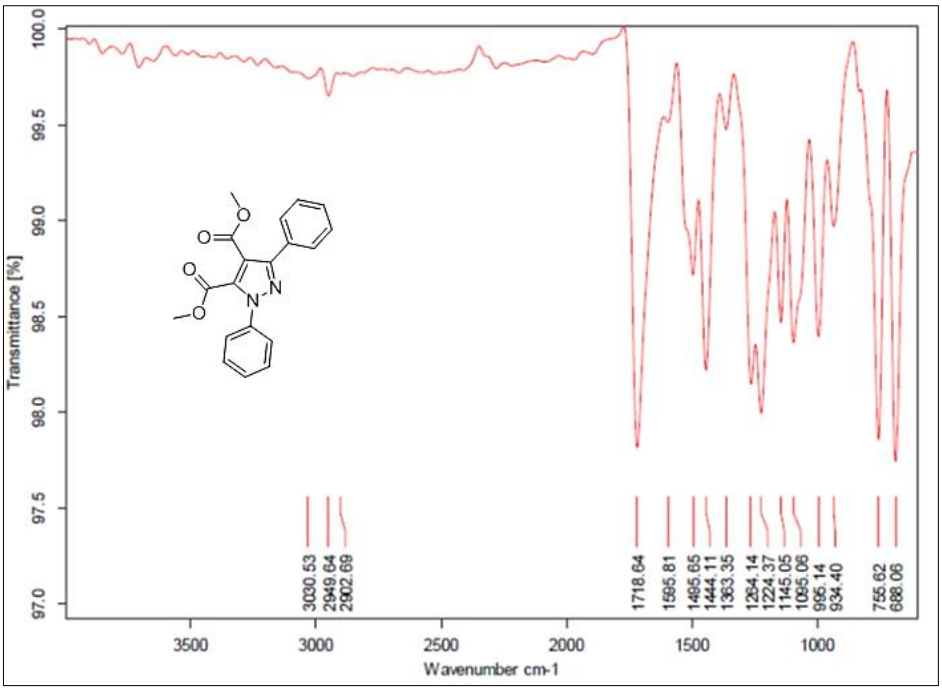


Figure 2.21 FTIR spectrum of **2.3ab**

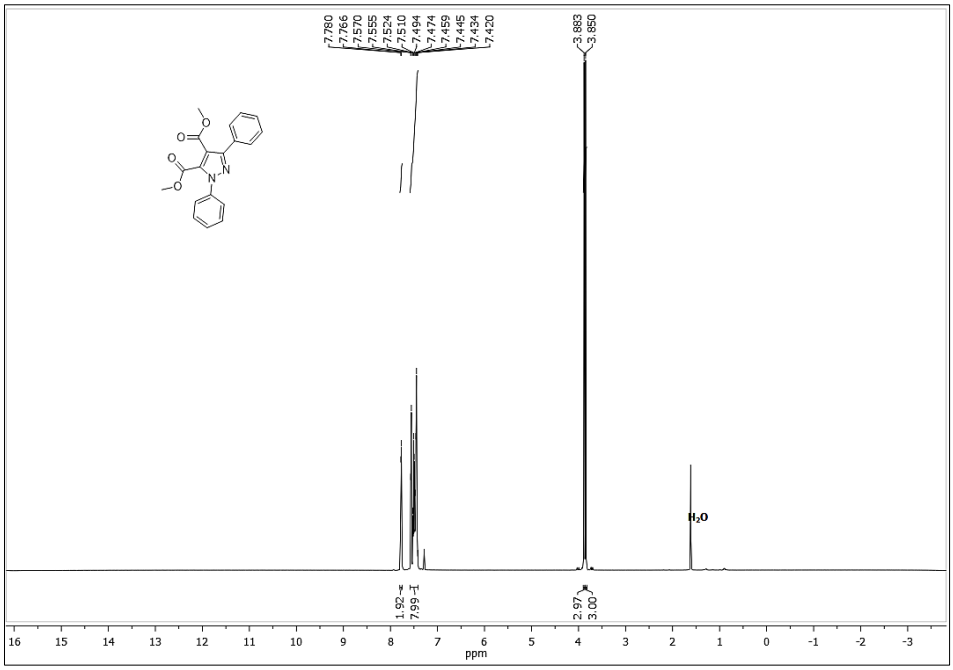


Figure 2.22 ^{1}H NMR spectrum of **2.3ab**

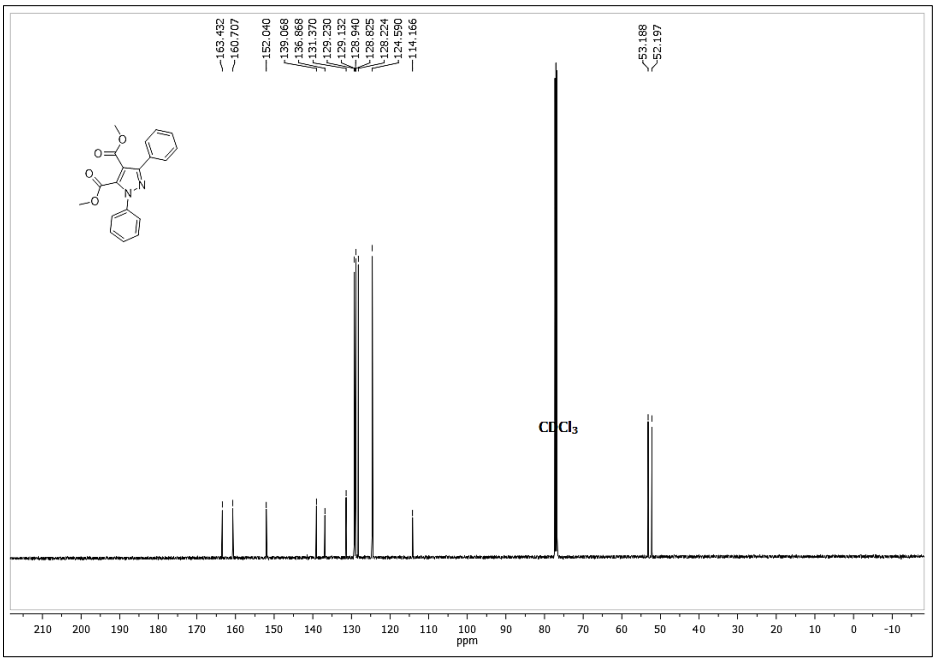


Figure 2.23 ^{13}C NMR spectrum of **2.3ab**

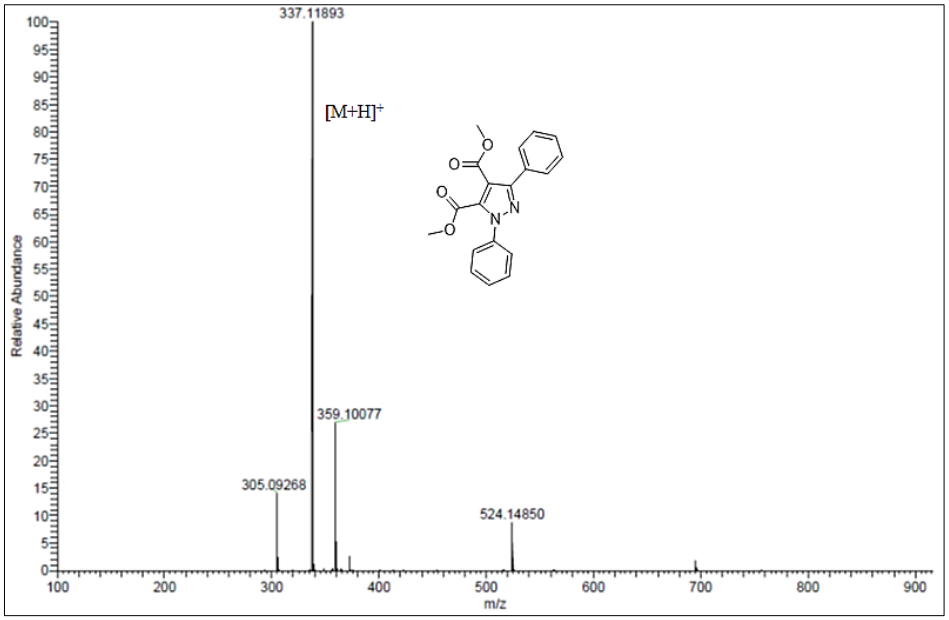


Figure 2.24 HRMS spectrum of **2.3ab**

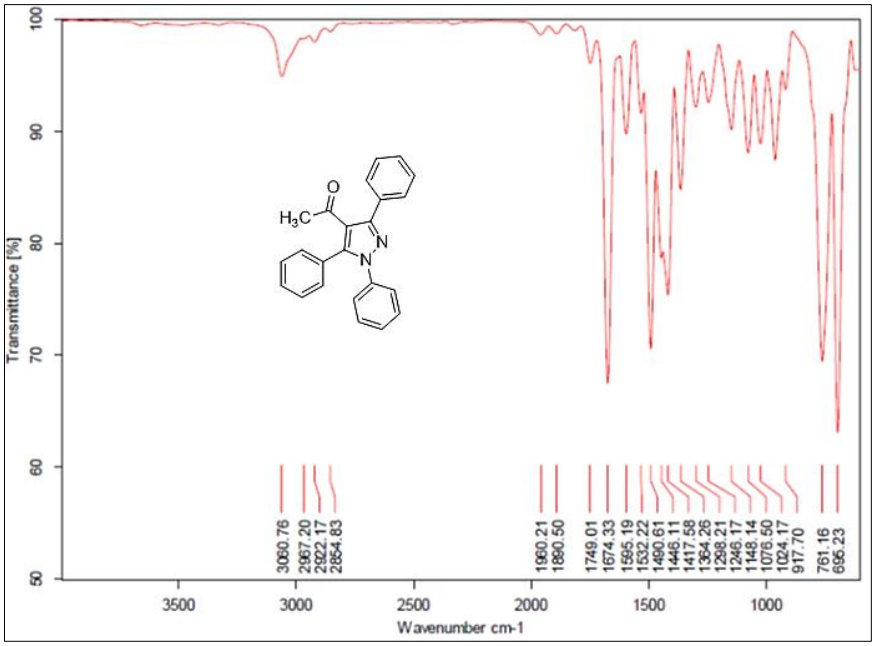


Figure 2.25 FTIR spectrum of **2.3ae**

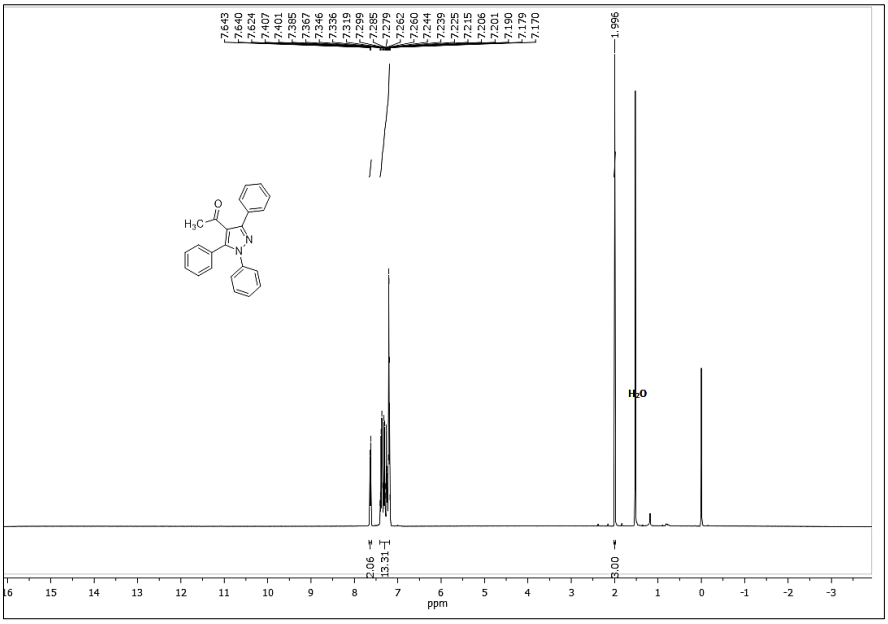


Figure 2.26 ^{1}H NMR spectrum of **2.3ae**

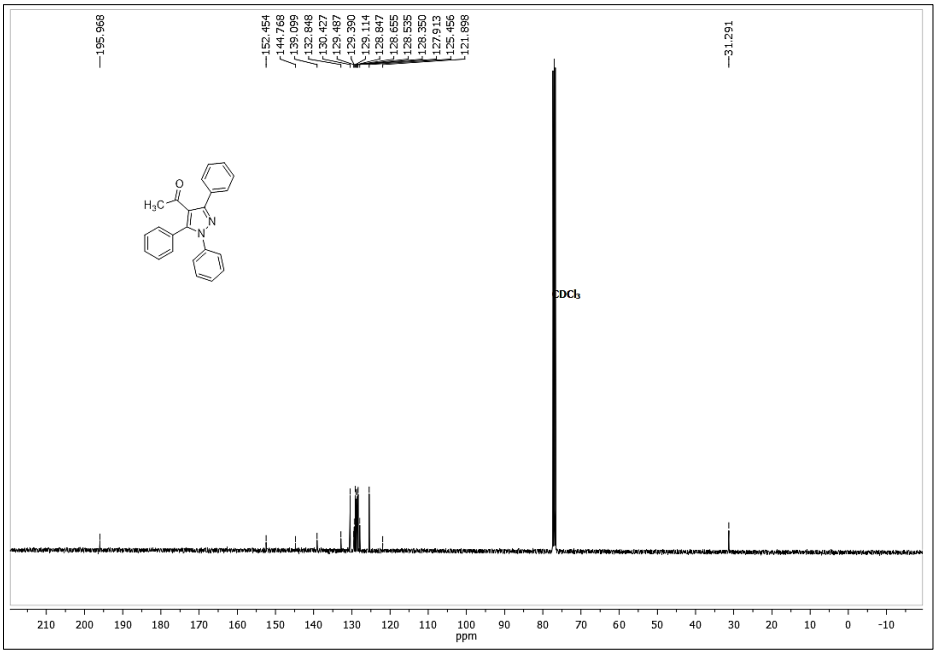


Figure 2.27 ^{13}C NMR spectrum of **2.3ae**

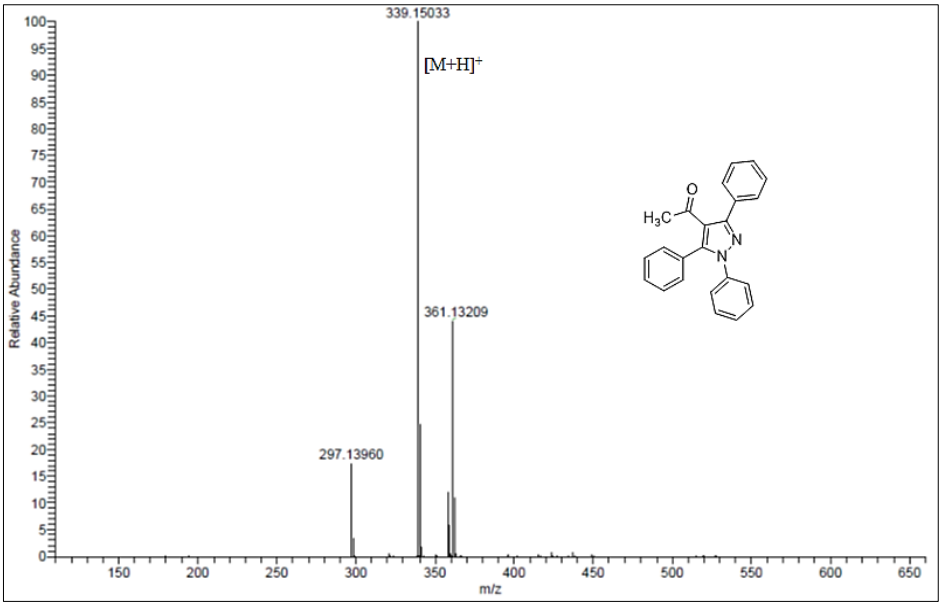


Figure 2.28 HRMS spectrum of **2.3ae**

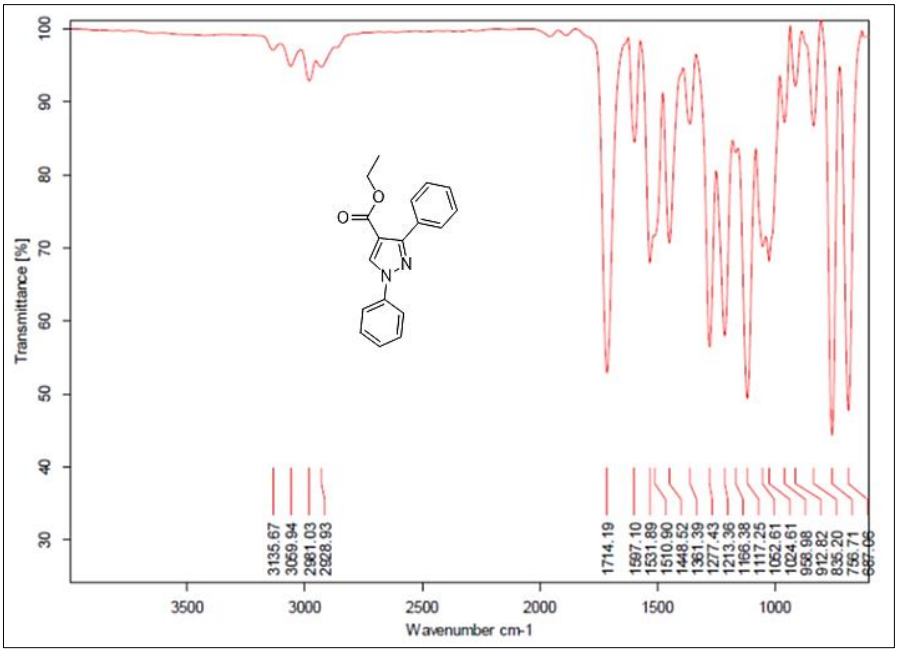


Figure 2.29 FTIR spectrum of **2.3ad**

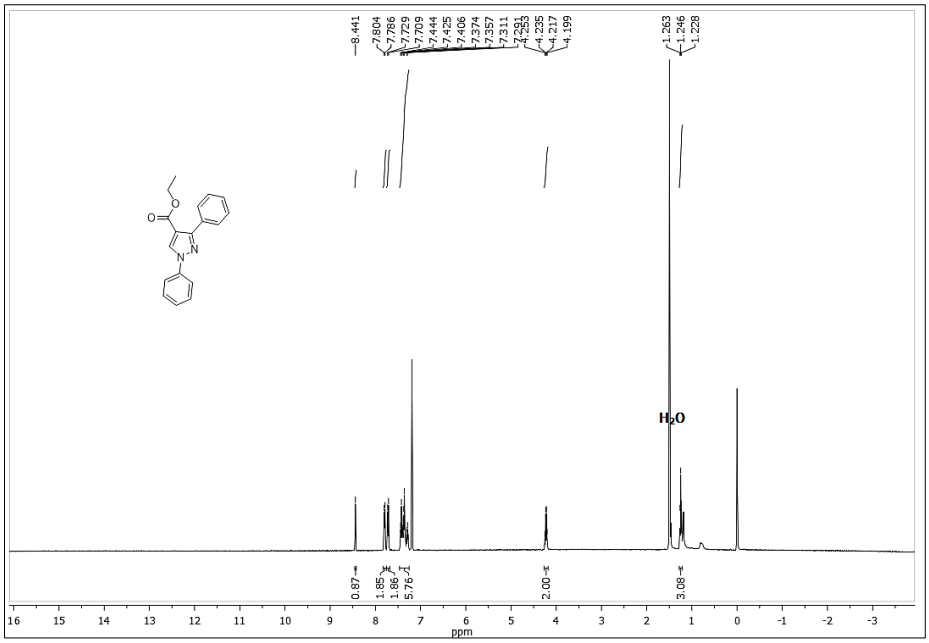


Figure 2.30 ^{1}H NMR spectrum of **2.3ad**

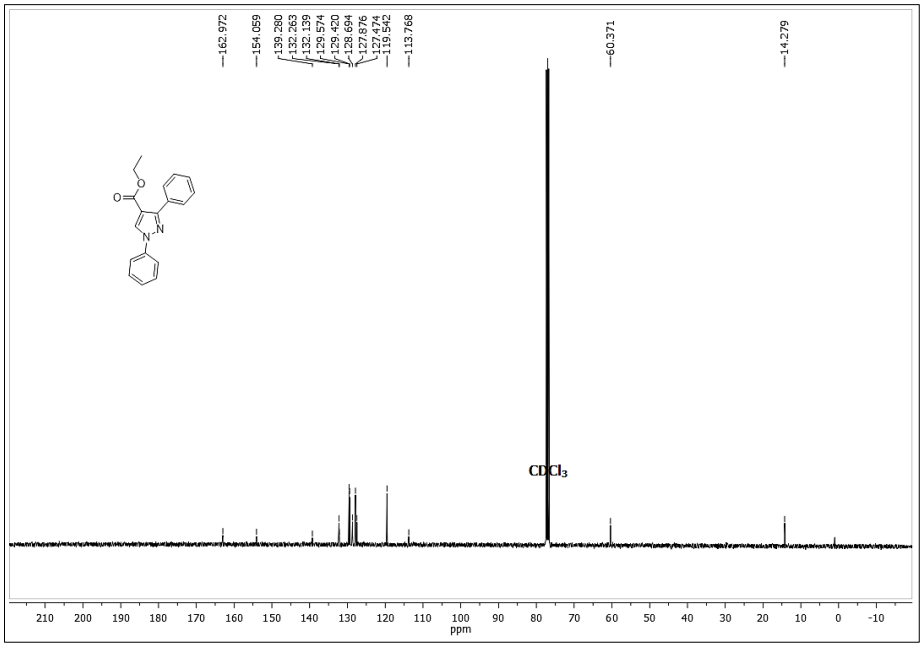


Figure 2.31 ^{13}C NMR spectrum of **2.3ad**

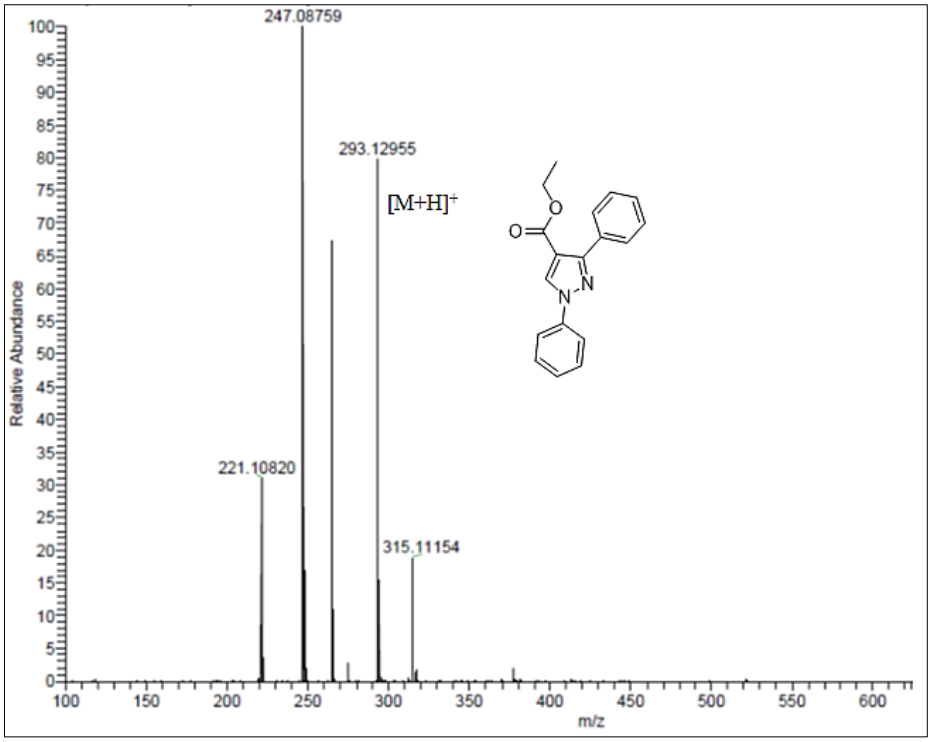


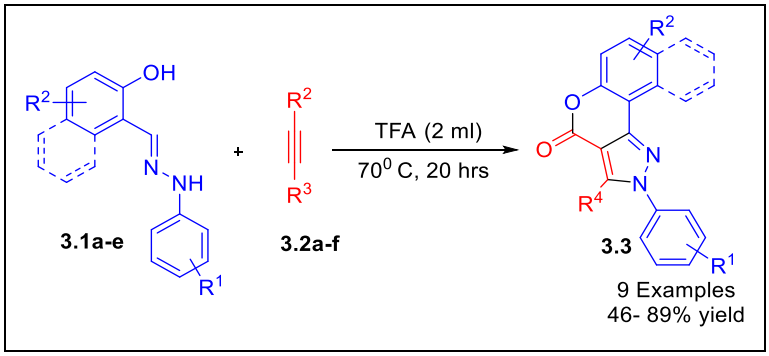
Figure 2.32 HRMS spectrum of **2.3ad**

CHAPTER 3

DIPOLAR CYCLOADDITION OF SALICYLALDEHYDE HYDRAZONES TO ACETYLENIC ESTERS FOR THE DIRECT SYNTHESIS OF CHROMENOPYRAZOLE

Abstract

A selective synthesis of a fused polycycle- chromenopyrazole in one-pot was described. Intramolecular lactonization of aryl hydroxyl group to the adjacent ester group take place at elevated temperature in a metal-free condition. Salicylaldehyde hydrazones and 2-hydroxyl naphthaldehyde hydrazones annulated across acetylenic esters with various substitution patterns.



3.1 INTRODUCTION

Synthetic routes that sequentially involve multiple bond-formation are beneficial in organic synthesis. Such methods offer rapid access to complex molecular scaffolds cost-effectively compared to the conventional step-wise routes. (Taylor et al. 2016). Hybrid compounds provide a substantial contribution to the advancement of pharmacology. Hybrid molecules are usually a combination of two or more biologically active molecules fused in a polycycle that generally show an enhanced performance compared to their building units in their biological activity (Medina et al. 2015; Meunier 2007; de Moliner et al. 2017; Tietze et al. 2003). The synthesis of hybrid heterocycles is always challenging due to various bond formation sequences that demand high atom and step-economy. The technique would be more appealing if multiple bond-formation sequences occurred in a one-pot manner.

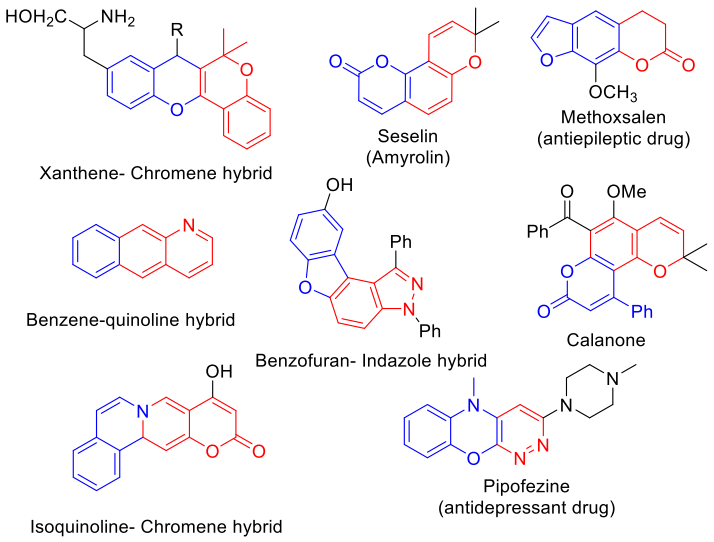
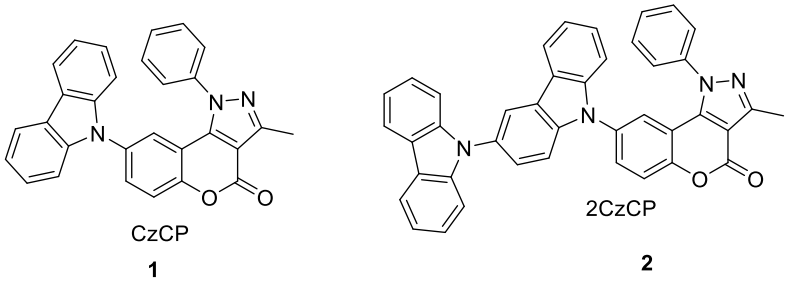


Figure 3.1 Representative examples of hybrid polycycles

3.2 APPLICATIONS OF CHROMENOPYRAZOLES AND THEIR DERIVATIVES

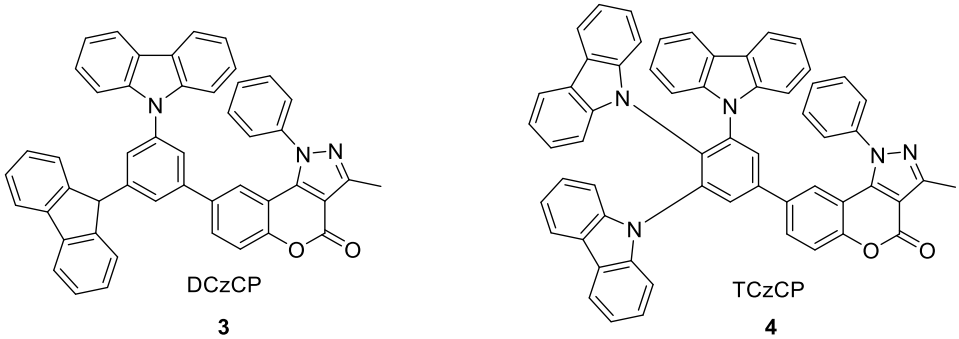
Pyrazoles and chromenes are prominent structural motifs with diverse reactivity, and hence chromenopyrazoles, a hybrid molecule of pyrazole and chromene, are potent scaffolds for diverse applications. The synthesis of this core has always been appealing because of its synthetic applications in medicinal chemistry, industrial research, photovoltaics, etc.

For the first time, chromenopyrazole (CP) was employed as an electron-acceptor core to develop and manufacture two new blue bipolar hosts by Mallesham Godumala et al. in 2018. The effect of donor strength on photophysical, electrochemical, and electroluminescent properties was studied in depth. Both the molecules were observed to have high triplet energy (3.0 eV) with the proper HOMO and LUMO energy levels. As a result, OLEDs with CzCP as a host in the emissive layer achieved excellent performance with an external quantum efficiency of 27.9%(Godumala et al. 2018).



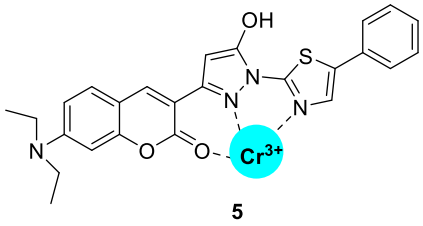
Scheme 3.1

The same group in 2019, designed and synthesized two new bipolar host materials. Both materials were used as hosts by doping a known green thermally activated delayed fluorescent (TADF) emitter in solution-processable OLEDs. With a maximum external quantum efficiency (EQE) of 21.2 percent, DCzCP- based devices provide the best performance (Godumala et al. 2019).



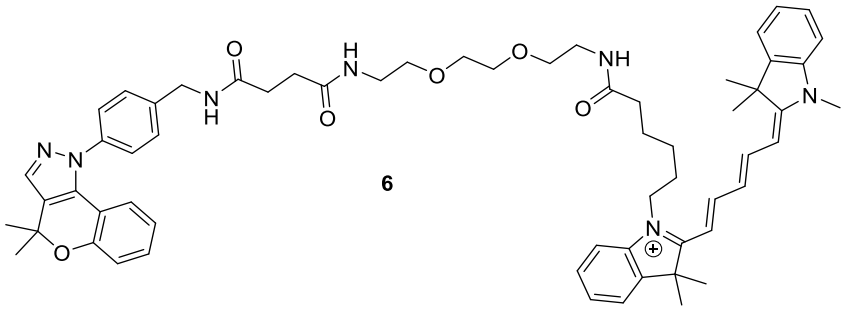
Scheme 3.2

A coumarin- pyrazole probe for detecting chromium ions via fluorescent mode was designed and synthesized by Kailasam Saravana Mani and co-workers in 2018. The synthesized compound selectively detects chromium ions in distinct ratiometric absorption and fluorescence response. Chelation-enhanced quenching in DMSO medium accounts for the selectivity toward Cr^{3+} ions. As a result, the fluorescent probe was used in A-549 cells to perform fluorescence bioimaging of Cr^{3+} ions under physiological settings (Saravana Mani et al. 2018).



Scheme 3.3

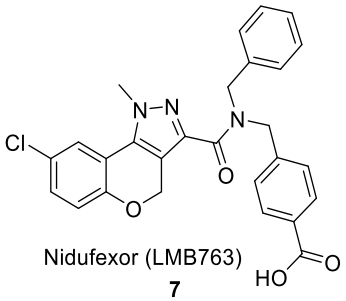
Sameek Singh et al. in 2019 reported a series of chromenopyrazole-based CB_2R fluorescent ligands, which is a promising target for pain and inflammatory diseases therapy. Among the chromenopyrazole derivatives synthesized, compound **6** was the fluorescent ligand with high affinity. According to widefield imaging tests **6** binds to CB_2R in living cells with good selectivity and low levels of non-specific fluorescence, and it also shows high affinity, selectivity, and imaging capabilities (Singh et al. 2019).



6

Scheme 3.4

A tricyclic dihydrochromenopyrazole core-based non-bile acid FXR agonist for the treatment of non-alcoholic steatohepatitis was developed by Donatella Chianelli and co-workers in 2020. These synthesized compounds could generate nidufexor (LMB763), which shows FXR- dependent gene modulation in vivo and partial FXR agonistic activities in vitro. In patients with NASH and diabetic nephropathy, Nidufexor has moved to Phase 2 human clinical studies (Chianelli et al. 2020).

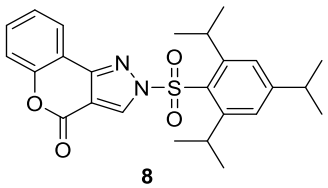


Nidufexor (LMB763)

7

Scheme 3.5

The in vitro anticancer studies for developing new PI3Kα inhibitors based on chromeno[4,3-c]pyrazol-4(2H)-one derivative, were carried out by Yong Yin and his group in 2019. Most of the designed compounds have better antiproliferative properties against four cancer cell lines. Among the synthesized compounds, compound **8** shows high selectivity against PI3Kα protein (Yin et al. 2019).



8

Scheme 3.6

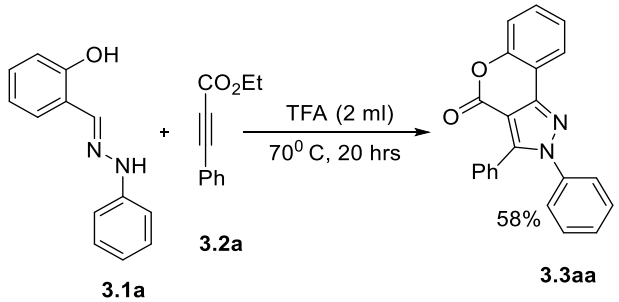
Due to the extended scope of the chromenopyrazole moiety in various fields, it is extremely desirable to develop a cost-effective and straightforward one-pot synthesis

of this hybrid heteroaromatic polycycle from readily available starting materials. Biologically active scaffolds based on chromenopyrazole are also plenty, and hence the development of new synthetic routes for their synthesis has always fascinated chemists.

3.3 PRESENT WORK

Encouraged by the previous result obtained from the reaction between aryl hydrazones and acetylenic esters, we examined the scope of this reaction with salicylaldehyde hydrazones. Here we envisioned the feasibility of an intramolecular cyclization between the phenolic -OH and the ester group in the initially formed pyrazole so that the final product would be a substituted chromenopyrazole a hybrid molecule.

We prepared several hydrazones from salicylaldehyde and 2-hydroxy naphthaldehyde and treated them with acetylenic esters, both symmetric and unsymmetrical ones in TFA. Initially, the reaction between salicylaldehyde hydrazone (**3.1a** 0.5 mmol, 106 mg) and ethyl phenyl propiolate (**3.2a**) was carried out in TFA at room temperature, following the previous procedure. However, at room temperature, the initially formed pyrazole failed to lactonize, and the expected chromenopyrazole derivative was not observed even after 12 h. So the reaction was repeated at an elevated temperature of 70°C, and as expected, the lactonization was complete at 70°C and afforded only the final chromenopyrazole without a trace of the initial pyrazole derivative. The newly formed compound, 2, 3-diphenylchromeno[4,3-c]pyrazol-4(2H)-one (**3.3aa**), was isolated as a white solid in 58% yield. The structure of the product was unambiguously confirmed using FT-IR, NMR, and HR-MS techniques.



Scheme 3.7

The IR absorption band at 1725 cm^{-1} of compound **3.3aa** corresponds to the C=O stretching frequency of the lactone ring (**Figure 3.2**). The absence of the –OH proton and aliphatic protons confirms the lactonization process. All the fourteen protons of the

compound resonate in the aromatic region from δ= 8.21- 7.34 ppm (**Figure 3.3**). The carbonyl carbon atom resonates at δ= 157.8 ppm, all other resonance signals in the ^{13}C NMR spectrums are observed within the aromatic region of 153.0 ppm to 106.1 ppm (**Figure 3.4**). The HR-MS obtained for the compound is in good agreement with the expected value (**Figure 3.5**).

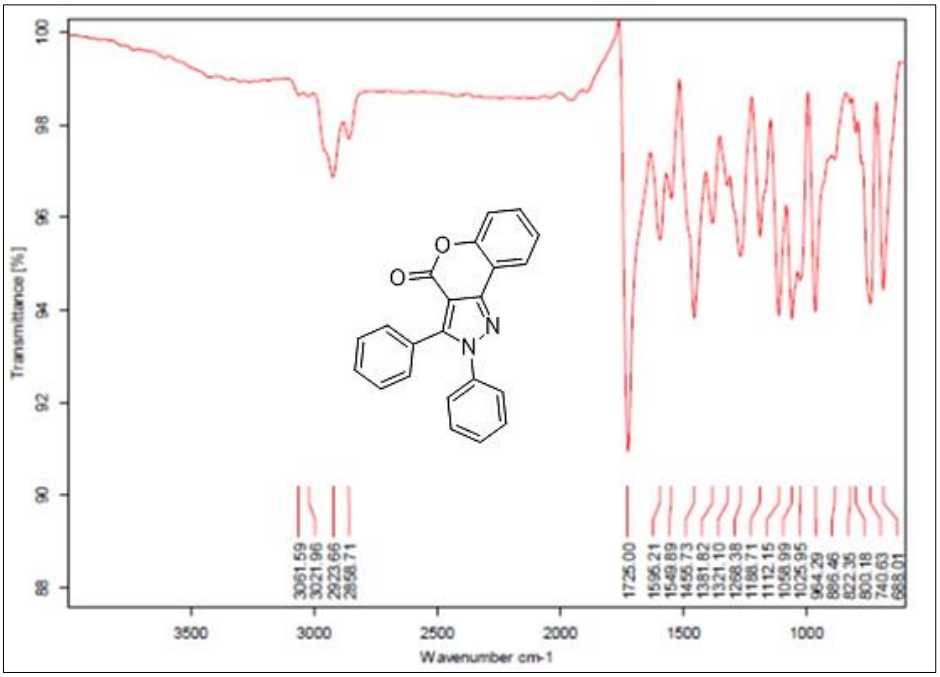


Figure 3.2 FTIR spectrum of **3.3aa**

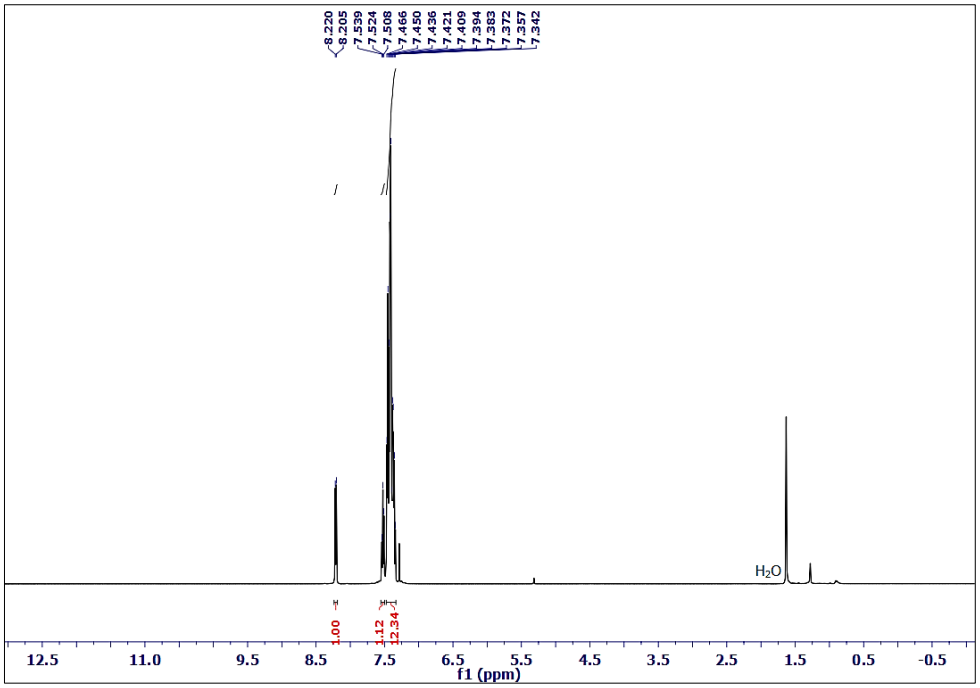


Figure 3.3 ^{1}H NMR spectrum of **3.3aa**

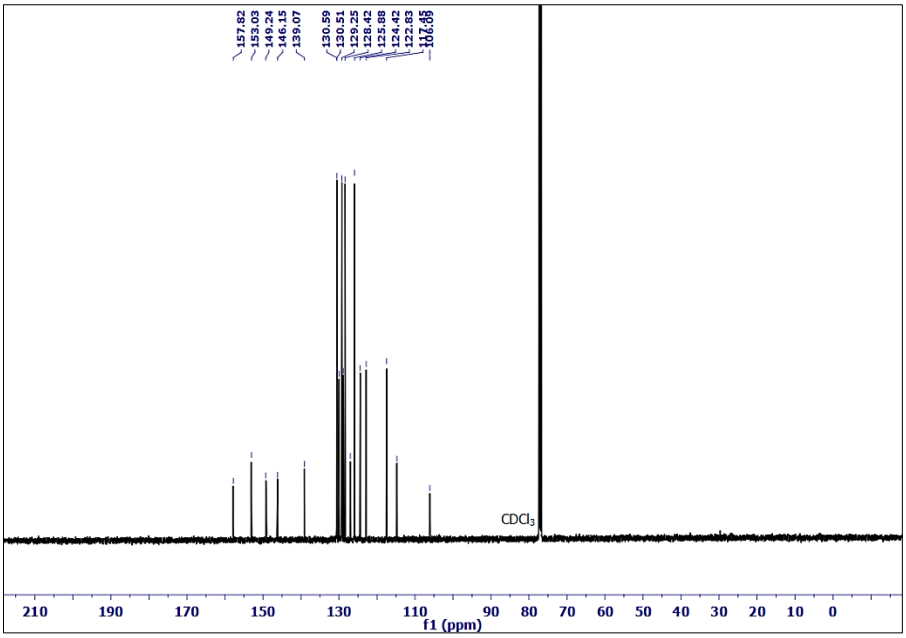


Figure 3.4 ^{13}C NMR spectrum of **3.3aa**

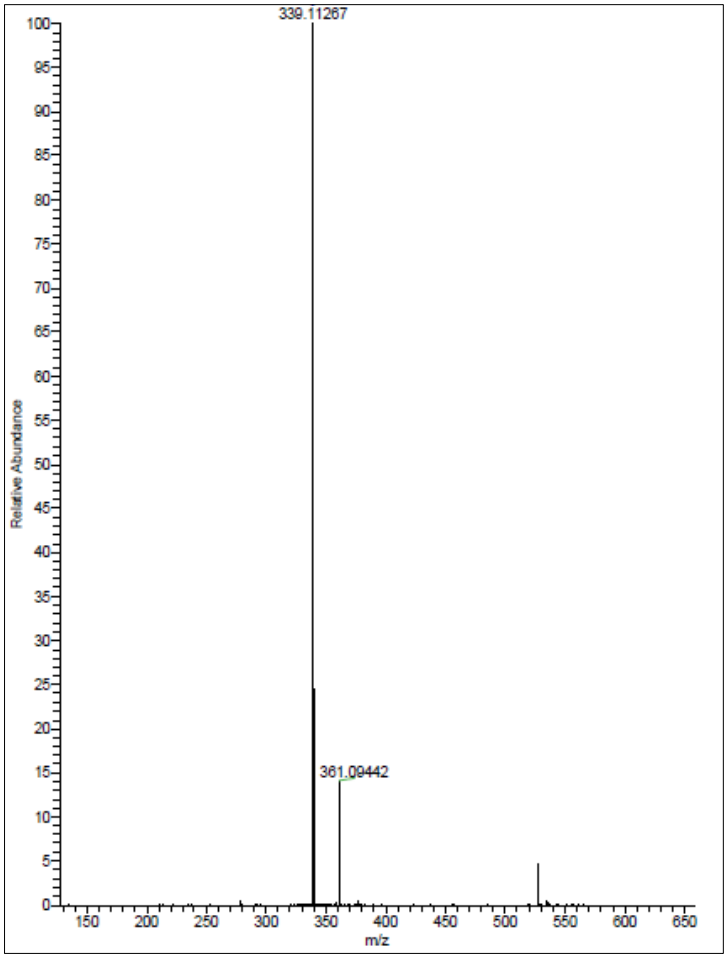
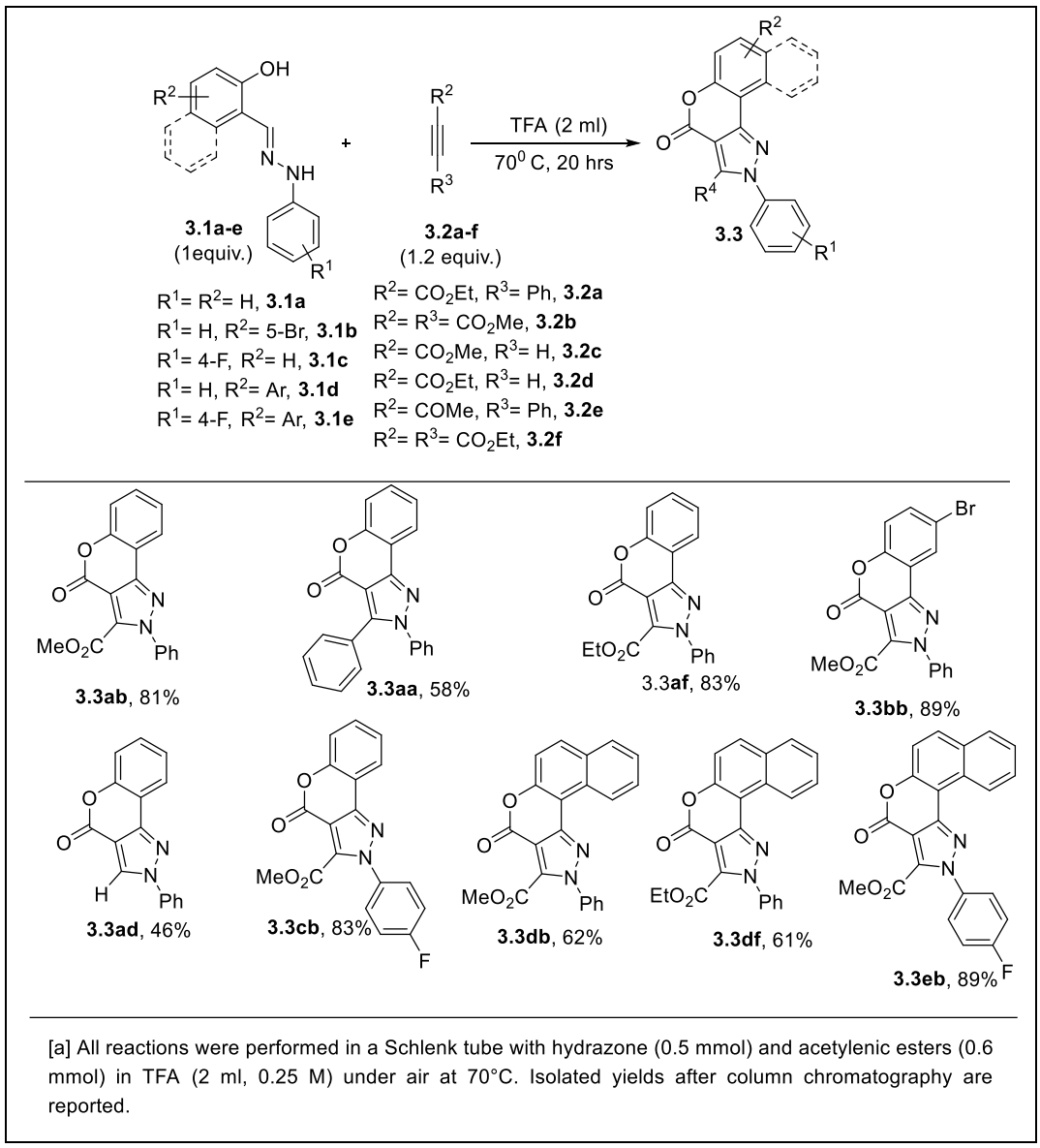


Figure 3.5 HRMS spectrum of **3.3aa**

3.4 SUBSTRATE SCOPE OF THE REACTION

Under the optimized condition, the substrate scope of the reaction was monitored. The versatility of the reaction was studied by taking variously substituted salicylaldehyde hydrazones, 2- hydroxyl naphthaldehyde hydrazones, and acetylenic esters. Several chromenopyrazole derivatives were isolated in good yields. Irrespective of the electronic nature of the substituents on the aromatic ring, all the synthesized salicylaldehyde hydrazones and 2- hydroxyl naphthaldehyde hydrazones reacted with acetylenic esters. Halogen atoms on the aromatic rings of hydrazones were also compatible with the condition. Unsymmetrical ester- ethyl phenyl propiolate, symmetrical esters- DMAD and DEAD, yielded chromenopyrazoles at 70°C. Interestingly, in the case of terminal alkyne -ethyl propiolate, the reaction was complete at room temperature itself (**3.2ad**).



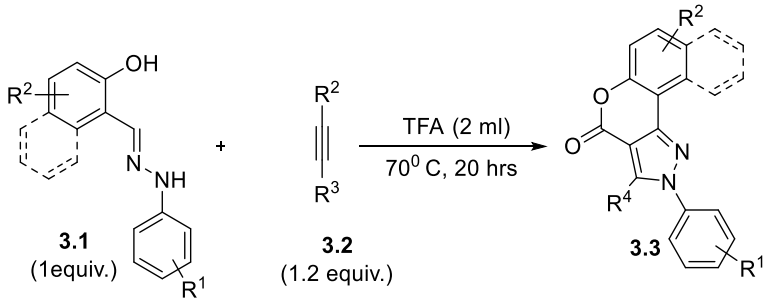
[a] All reactions were performed in a Schlenk tube with hydrazone (0.5 mmol) and acetylenic esters (0.6 mmol) in TFA (2 ml, 0.25 M) under air at 70°C. Isolated yields after column chromatography are reported.

Table 3.1 Chromenopyrazole derivatives synthesized

3.5 CONCLUSIONS

- We have developed an efficient, acid-promoted synthetic route for the synthesis of chromenopyrazole, a hybrid molecule with both pharmaceutical and material applications.
- The developed strategy selectively yields chromenopyrazoles in a metal-free, one-pot manner.
- Symmetrical alkynes such as DMAD and DEAD successfully cyclized to generate chromenopyrazoles in TFA (Compounds **3.3ab**, **3.3af**, **3.3bb**, **3.3cb**, **3.3db**, **3.3df** and **3.3eb**).
- Sterically hindered unsymmetrical acetylenic ester- ethyl phenyl propiolate also participated in the reaction and yielded the final product (Compound **3.3aa**).
- Surprisingly, the terminal alkynes ethyl propiolate and methyl propiolate reacted with salicylaldehyde hydrazones at room temperature itself to yield the chromenopyrazole **3.3ad**.
- Readily accessible starting materials and metal-free conditions are the key highlights of the proposed reaction.
- The solvent TFA proved to be highly compatible with the starting materials, and the developed methodology exhibited an excellent functional group tolerance.

3.6 GENERAL PROCEDURE FOR THE SYNTHESIS OF CHROMENOPYRAZOLE DERIVATIVES



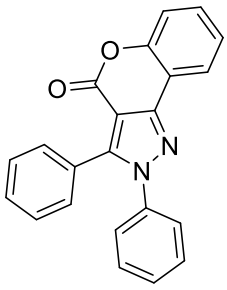
Scheme 3.8

Hydrazone (0.5 mmol, 1equiv.) was taken in an oven-dried Schlenk tube equipped with a magnetic stirrer. To this, alkyne (0.6 mmol, 1.2 equiv.) was added, followed by 2 ml TFA (solvent). The reaction mixture was heated at 70^0C in an oil bath for about 20 h with continuous monitoring by checking TLC. The reaction mixture was then washed

with saturated $NaHCO_3$ solution, and the organic layer was extracted in ethyl acetate. The ethyl acetate layer was finally washed with brine solution and distilled water. Dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was purified by silica gel column chromatography using pet ether-ethyl acetate as eluent.

3.7 ^{1}H NMR, ^{13}C NMR AND HRMS SPECTRAL DATA OF SYNTHESIZED CHROMENOPYRAZOLES

3.7.1. 2,3-diphenylchromeno[4,3-c]pyrazol-4(2H)-one (3.3aa): Following the general procedure, the reaction between 2-((2-phenylhydrazono)methyl)phenol (0.5 mmol, 106 mg) with ethyl phenyl propiolate (0.6 mmol, 105 mg, 99.5 µl) yielded the desired product 2,3-diphenylchromeno[4,3-c]pyrazol-4(2H)-one as a white solid in 58% yield (97.7 mg).



Chemical Formula: $C_{22}H_{14}N_2O_2$

Melting point 222-224°C.

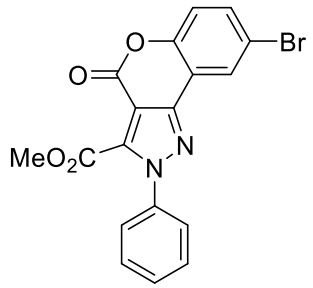
FT-IR (ATR): ν_{max}= 3021, 2923, 2858, 1725, 1595, 1549, 1455, 1381, 1321, 1268, 1188, 1112, 1058, 1025 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.21 (s, 1H), 7.54– 7.34 (m, 13H) ppm

^{13}C NMR (125 MHz, $CDCl_3$) δ = 157.8, 153.0, 149.2, 146.1, 139.1, 130.6, 130.5 (2 C), 130.0, 129.2 (2 C), 128.9, 128.4 (2 C), 127.0, 125.8 (2 C), 124.4, 122.83, 117.4, 114.8, 106.1 ppm

HRMS (ESI) calcd for $C_{22}H_{14}N_2O_2$ $[M+H]^+$ 339.1128 found 339.1127.

3.7.2. Methyl-8-bromo-4-oxo-2-phenyl-2,4-dihydrochromeno[4,3-c]pyrazole-3-carboxylate (3.3bb): Following the general procedure, the reaction between 4-Bromo-2-((2-phenylhydrazono)methyl)phenol (0.5 mmol, 145 mg) with dimethyl acetylene dicarboxylate (0.6 mmol, 85.2 mg, 73.45 µl) yielded the desired product methyl-8-bromo-4-oxo-2-phenyl-2,4-dihydrochromeno[4,3-c]pyrazole-3-carboxylate as a white solid in 89% yield (177 mg).



Chemical Formula: $C_{18}H_{11}BrN_2O_4$

Melting point 94- 96° C.

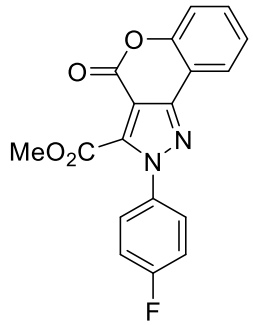
FT-IR (ATR): ν_{max}= 3101, 3027, 2957, 1731, 1590, 1551, 1492, 1437, 1376, 1306, 1228, 1141, 1092 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.23 (s, 1H), 7.55- 7.48 (m, 4H), 7.23- 7.19 (m, 3H), 3.88 (s, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ= 159.2, 155.4, 151.9, 147.9, 138.8, 136.0, 133.9, 130.0, 129.5 (2 C), 125.7, 124.7 (2 C), 119.3, 117.5, 115.7, 108.2, 53.7 ppm

HRMS (ESI) calcd for $C_{18}H_{11}BrN_2O_4$ $[M+Na]^+$ 420.9794 found 420.9805.

3.7.3 Methyl-2-(4-fluorophenyl)-4-oxo-2,4-dihydrochromeno[4,3-c]pyrazole-3-carboxylate (3.3cb): Following the general procedure, the reaction between 2-((2-(4-fluorophenyl)hydrazono)methyl)phenol (0.5 mmol, 115 mg) with dimethyl acetylene dicarboxylate (0.6 mmol, 85.2 mg, 73.45 μl) yielded the desired product Methyl-2-(4-fluorophenyl)-4-oxo-2,4-dihydrochromeno[4,3-c]pyrazole-3-carboxylate as a white solid in 83% yield (140 mg).



Chemical Formula: $C_{18}H_{11}FN_2O_4$

Melting point 226-228°C.

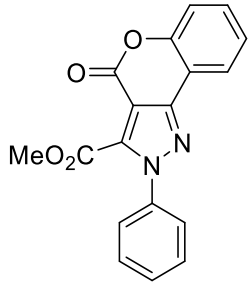
FT-IR (ATR): ν_{max}= 3055, 1750, 1721, 1607, 1561, 1504, 1443, 1321, 1225, 1143, 1089, 1031 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ= 8.06 (dd, *J* = 7.5 Hz, 1.5 Hz, 1H), 7.51 – 7.44 (m, 3H), 7.34 (d, *J* = 8.5 Hz, 1H), 7.28 (t, J= 7.5 Hz, 1H), 7.20- 7.15 (m, 2H), 3.89 (s, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ= 163.1 ($^1J_{CF}$= 249.4 Hz), 159.3, 155.9, 153.0, 149.2, 135.9, 135.0 ($^4J_{CF}$= 3.3 Hz), 131.2, 127.0 ($^3J_{CF}$= 8.9 Hz, 2 C), 124.7, 123.0, 117.6, 116.5 ($^2J_{CF}$= 23.2 Hz, 2 C), 113.8, 108.3, 53.7 ppm

HRMS (ESI) calcd for $C_{18}H_{11}FN_2O_4$ $[M+Na]^+$ 361.0595 found 361.0604.

3.7.4. Methyl-4-oxo-2-phenyl-2,4-dihydrochromeno[4,3-c]pyrazole-3-carboxylate (3.3ab): Following the general procedure, the reaction between 2-((2-phenylhydrazono)methyl)phenol (0.5 mmol, 106 mg) with dimethyl acetylene dicarboxylate (0.6 mmol, 85.2 mg, 73.45 µl) yielded the desired product methyl-4-oxo-2-phenyl-2,4-dihydrochromeno[4,3-c]pyrazole-3-carboxylate as a white solid in 81% yield (129.8 mg).



Chemical Formula: $C_{18}H_{12}N_2O_4$

Melting point 188-190°C.

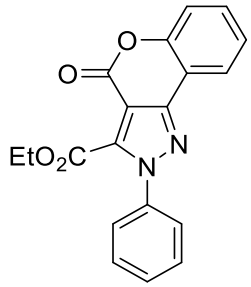
FT-IR (ATR): ν_{max}= 3052, 2953, 1719, 1594, 1551, 1492, 1440, 1392, 1316, 1228, 1138, 1093, 1028 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ= 8.09 (dd, J= 8 Hz, 1.2 Hz, 1H), 7.52-7.43 (m, 6H), 7.36-7.34 (m, 1H), 7.28 (t, J= 8 Hz, 1H), 3.88 (s, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ= 158.5, 155.1, 152.0, 148.1, 137.9, 130.0, 128.9, 128.4 (2C), 123.8 (2C), 123.7, 121.9, 116.5, 113.0, 52.6 ppm

HRMS (ESI) calcd for $C_{18}H_{12}N_2O_4$ $[M+Na]^+$ 343.0689 found 343.0706.

3.7.5. Ethyl-4-oxo-2-phenyl-2,4-dihydrochromeno[4,3-c]pyrazole-3-carboxylate (3.3af): Following the general procedure, the reaction between 2-((2-phenylhydrazono)methyl)phenol (0.5 mmol, 106 mg) with diethyl acetylene dicarboxylate (0.6 mmol, 102 mg, 95.95 µl) yielded the desired product ethyl-4-oxo-2-phenyl-2,4-dihydrochromeno[4,3-c]pyrazole-3-carboxylate as a white solid in 83% yield (139.2 mg).



Chemical Formula: $C_{19}H_{14}N_2O_4$

Melting point 116- 118° C.

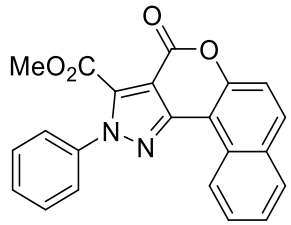
FT-IR (ATR): ν_{max}= 3066, 2979, 2919, 1750, 1712, 1601, 1558, 1484, 1445, 1380, 1314, 1233, 1141, 1090, 1025 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.17 (d, *J* = 7.8 Hz, 1H), 7.60 – 7.52 (m, 6H), 7.43 (d, *J* = 8 Hz, 1H), 7.36 (t, *J* = 7.5 Hz, 1H), 4.43 (q, *J* = 14 Hz, 7 Hz, 2H), 1.29 (t, *J* = 7 Hz, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ = 158.9, 156.1, 153.1, 149.1, 139.0, 136.3, 131.0, 129.9, 129.4 (2 C), 124.9 (2 C), 124.7, 123.0, 117.6, 114.0, 108.2, 63.2, 13.7 ppm

HRMS (ESI) calcd for $C_{19}H_{14}N_2O_4$ $[M+H]^+$ 335.1026 found 335.1036.

3.7.6. Methyl-4-oxo-2-phenyl-2,4-dihydrobenzo[5,6]chromeno[4,3-c]pyrazole-3-carboxylate (3.3db): Following the general procedure, the reaction between 1-((2-phenylhydrazono)methyl)naphthalen-2-ol (0.5 mmol, 131 mg) with dimethyl acetylene dicarboxylate (0.6 mmol, 85.2 mg, 73.45 μl) yielded the desired product Methyl-4-oxo-2-phenyl-2,4-dihydrobenzo[5,6]chromeno[4,3-c]pyrazole-3-carboxylate as a white solid in 62% yield (114.8 mg).



Chemical Formula: $C_{22}H_{14}N_2O_4$

Melting point 208-210°C.

FT-IR (ATR): ν_{max}= 3071, 3022, 2922, 2854, 1754, 1588, 1539, 1499, 1302, 1227, 1148, 1103, 1024 cm^{-1}.

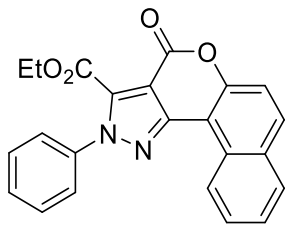
^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.52 (d, *J* = 8.8 Hz, 1H), 7.92 (d, *J* = 9.2 Hz, 1H), 7.87 (d, J= 8.4 Hz, 1H), 7.67 – 7.48 (m, 8H), 3.92 (s, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.9, 156.49, 152.5, 150.0, 139.1, 135.2, 132.0, 130.7, 129.8, 129.5 (2 C), 129.0, 128.5, 128.4, 126.7 (2 C), 126.0, 124.7, 117.6, 109.0, 108.07, 53.7 ppm

HRMS (ESI) calcd for $C_{22}H_{14}N_2O_4$ $[M+Na]^+$ 393.0846 found 393.0860.

3.7.7. Ethyl 4-oxo-2-phenyl-2,4-dihydrobenzo[5,6]chromeno[4,3-c]pyrazole-3-carboxylate (3.3df) : Following the general procedure, the reaction between 1-((2-phenylhydrazono)methyl)naphthalen-2-ol (0.5 mmol, 131 mg) with diethyl acetylene

dicarboxylate (0.6 mmol, 102 mg, 95.95 µl) yielded the desired product Ethyl 4-oxo-2-phenyl-2,4-dihydrobenzo[5,6]chromeno[4,3-c]pyrazole-3-carboxylate as a white solid in 61% yield (116.8 mg).



Chemical Formula: $C_{23}H_{16}N_2O_4$

Melting point 206-208°C.

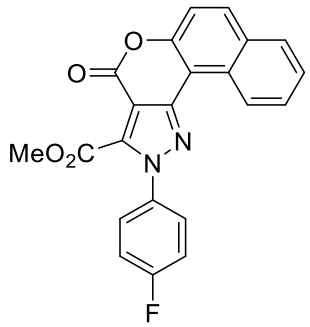
FT-IR (ATR): ν_{max}= 3064, 2924, 2856, 1745, 1628, 1540, 1499, 1434, 1380, 1337, 1301, 1220, 1151, 1025 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ = 9.52 (d, *J* = 8.8 Hz, 1H), 7.92 (d, *J* = 9.2 Hz, 1H), 7.87 (d, *J* = 7.6 Hz, 1H), 7.67- 7.48 (m, 8H), 4.38 (q, *J* = 14.4, 7.2 Hz, 2H), 1.23 (t, *J* = 7.2Hz, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ= 159.3, 156.4, 152.5, 149.9, 139.1, 135.7, 131.9, 130.6, 129.8, 129.4 (2 C), 129.0, 128.4(2C), 126.7, 125.9, 124.8 (2 C), 117.6, 108.9, 108.0, 63.2, 13.8 ppm

HRMS (ESI) calcd for $C_{23}H_{16}N_2O_4$ $[M+Na]^+$ 407.1002 found 407.1010.

3.7.8. Methyl 2-(4-fluorophenyl)-4-oxo-2,4-dihydrobenzo[5,6]chromeno[4,3-c]pyrazole-3-carboxylate (3.3eb) : Following the general procedure, the reaction between 1-((2-(4-fluorophenyl)hydrazono)methyl)naphthalen-2-ol (0.5 mmol, 140 mg) with dimethyl acetylene dicarboxylate (0.6mmol, 85.2 mg, 73.45 µl) yielded the desired product Methyl 2-(4-fluorophenyl)-4-oxo-2,4-dihydrobenzo[5,6]chromeno[4,3-c]pyrazole-3-carboxylate as a white solid in 89% yield (173.8 mg).



Chemical Formula: $C_{22}H_{13}FN_2O_4$

Melting point 236-238°C.

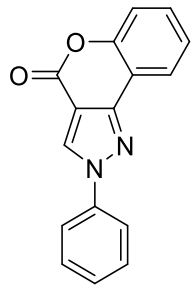
FT-IR (ATR): ν_{max}= 3088, 3017, 2922, 2853, 1757, 1722, 1690, 1618, 1588, 1544, 1515, 1457, 1443, 1390, 1328, 1302, 1230, 1149, 1104, 1081 $cm^{-1.}$

^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.48 (d, *J* = 8.8 Hz, 1H), 7.93 (d, *J* = 9.2 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.68 – 7.48 (m, 5H), 7.23 – 7.19 (m, 2H), 3.93 (s, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ = 163.1 ($^1J_{CF}$= 249.3 Hz), 159.7, 156.3, 152.5, 150.1, 135.3, 135.2 ($^4J_{CF}$= 3.3 Hz), 132.1, 130.7, 129.0, 128.5, 128.47, 126.8 ($^3J_{CF}$= 8.9 Hz, 2 C), 126.6, 126.0, 117.6, 116.5 ($^2J_{CF}$= 23.1 Hz, 2 C), 109.0, 107.9, 53.8 ppm

HRMS (ESI) calcd for $C_{22}H_{13}FN_2O_4$ $[M+Na]^+$ 411.0752 found 411.0771.

3.7.9. 2-phenylchromeno[4,3-c]pyrazol-4(2H)-one (3.3ad): Following the general procedure, the reaction between 2-((2-phenylhydrazono)methyl)phenol (0.5 mmol, 106 mg) with ethyl propiolate (0.6 mmol, 53 mg, 54.75 µl) yielded the desired product ethyl 3-(2-hydroxyphenyl)-1-phenyl-1*H*-pyrazole-4-carboxylate as a white solid in 46% yield (69.8 mg).



Chemical Formula: $C_{16}H_{10}N_2O_2$

Melting point 86-88°C.

FT-IR (ATR): ν_{max}= 3109, 3064, 1718, 1588, 1556, 1504, 1450, 1412, 1291, 1229, 1179, 1092, 1030 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.62(s, 1H), 8.12(d, J= 9 Hz, 1H), 7.78(d, J= 7.5 Hz, 2H), 7.50- 7.26 (m, 6H) ppm

^{13}C NMR (100MHz, $CDCl_3$) δ = 157.9, 153.1, 149.9, 139.2,, 130.7, 129.8 (2 C), 129.5, 128.6, 124.6, 122.9, 120.4 (2 C), 117.6, 114.6, 109.4 ppm

HRMS (ESI) calcd for $C_{16}H_{10}N_2O_2$ $[M+H]^+$ 263.0815 found 263.0821.

Appendix II

Representative FTIR, ^{1}H NMR, ^{13}C NMR and HRMS spectrum of some chromenopyrazole derivatives:

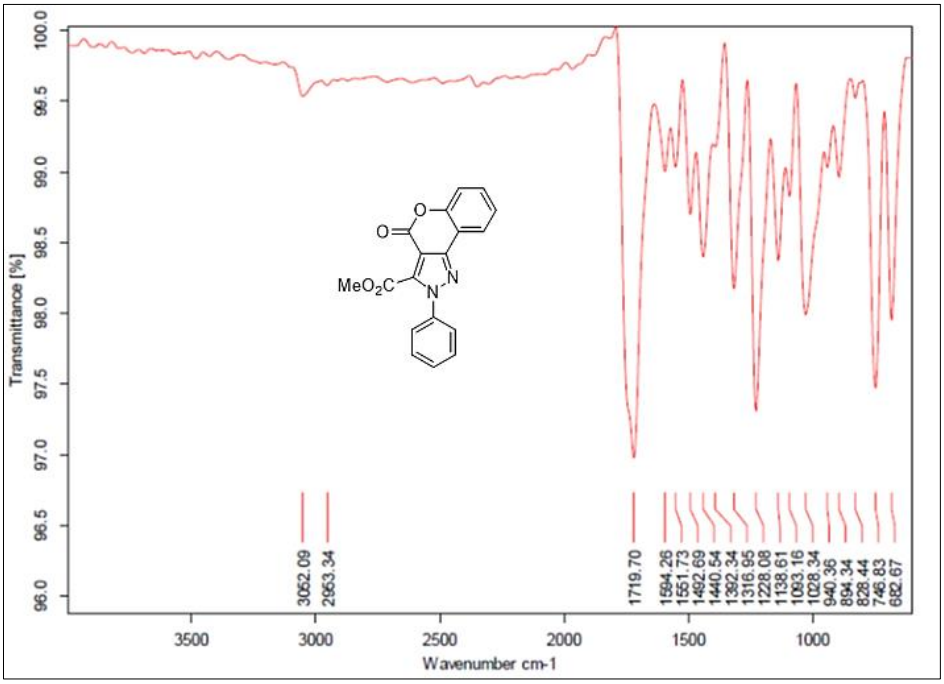


Figure 3.6 FTIR spectrum of **3.3ab**

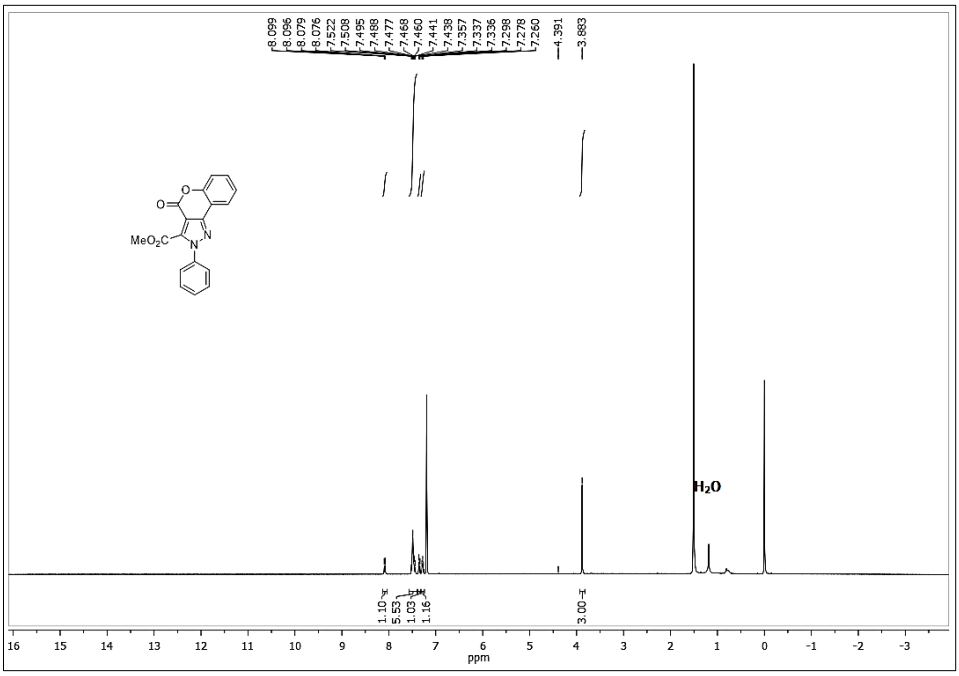


Figure 3.7 ^{1}H NMR spectrum of **3.3ab**

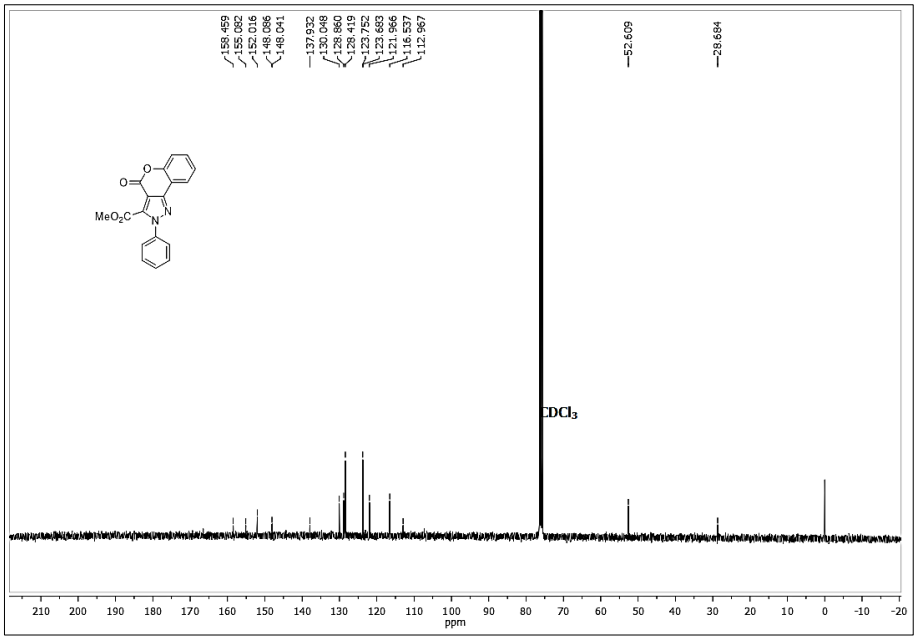


Figure 3.8 ^{13}C NMR spectrum of **3.3ab**

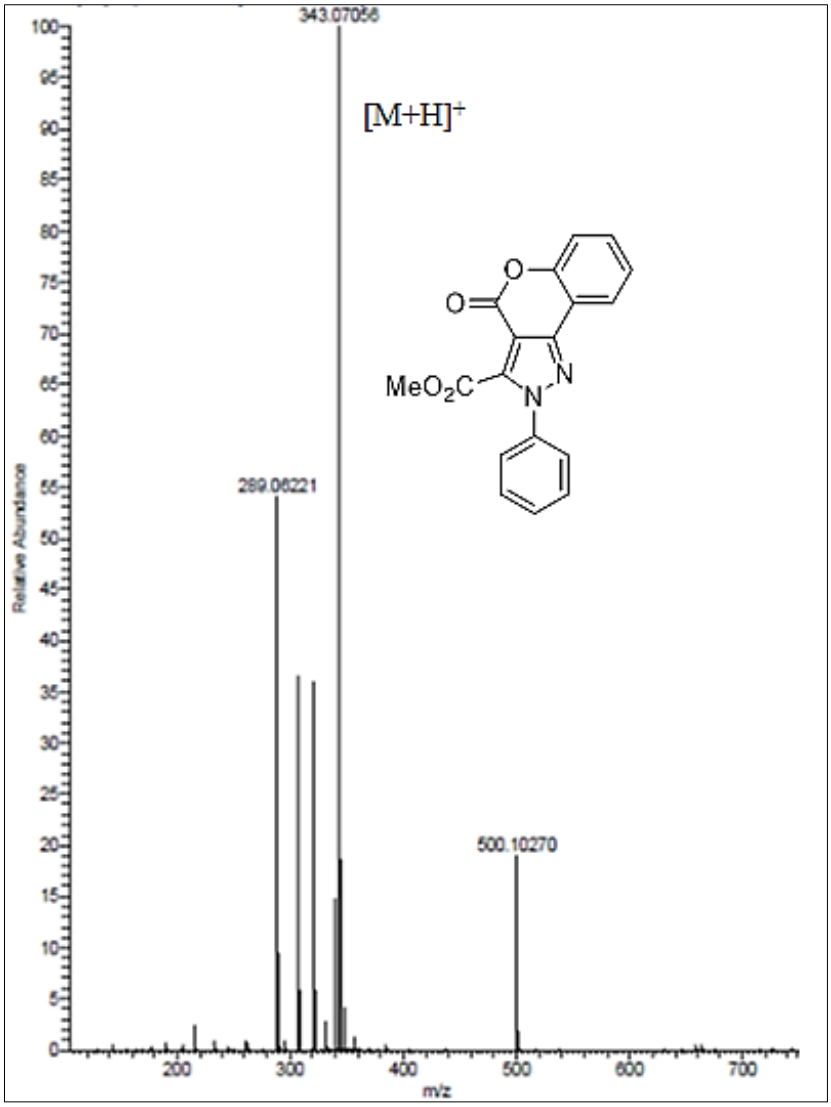


Figure 3.9 HRMS spectrum of **3.3ab**

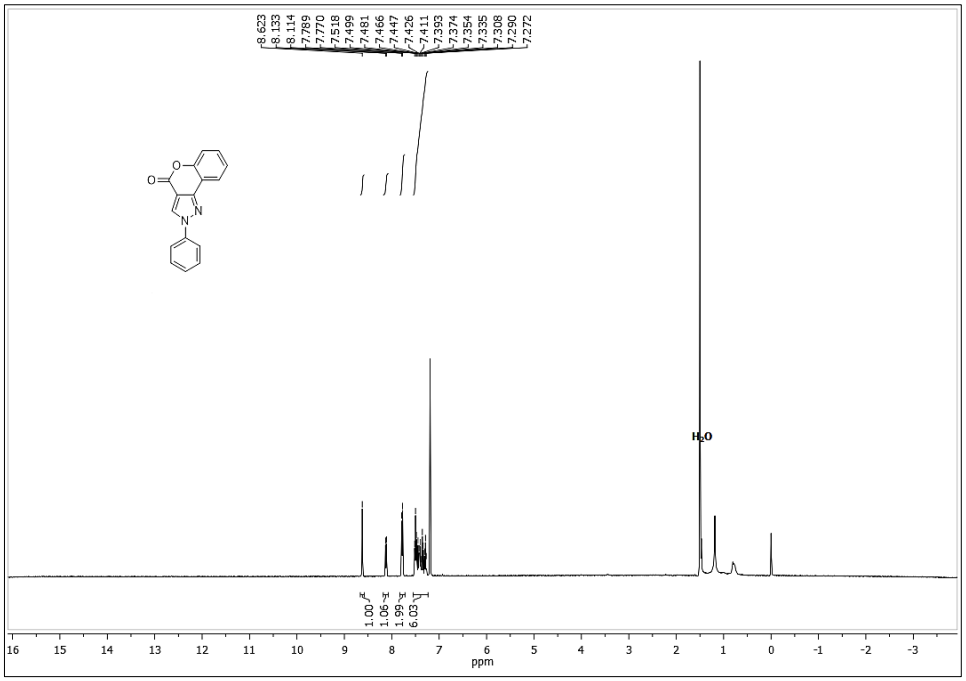


Figure 3.10 ^{1}H NMR spectrum of **3.3ad**

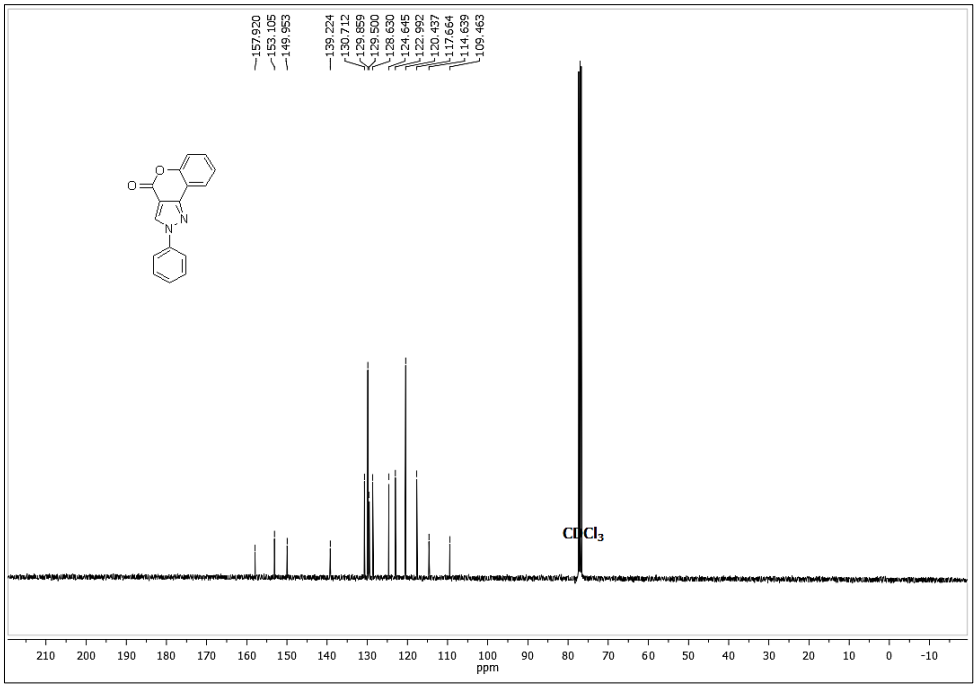


Figure 3.11 ^{13}C NMR spectrum of **3.3ad**

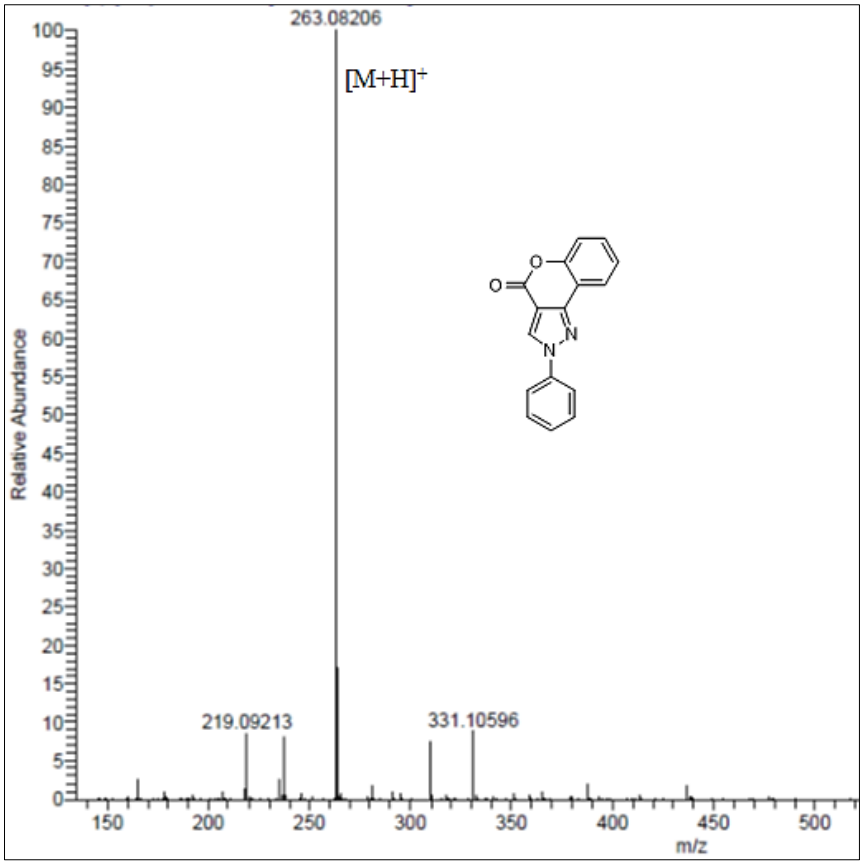


Figure 3.12 HRMS spectrum of **3.3ad**

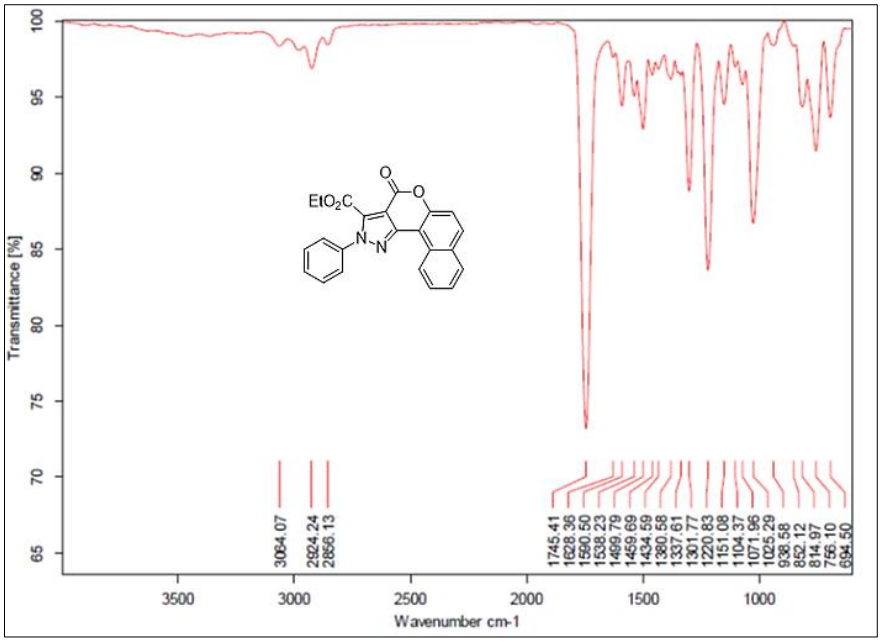


Figure 3.13 FTIR spectrum of **3.3df**

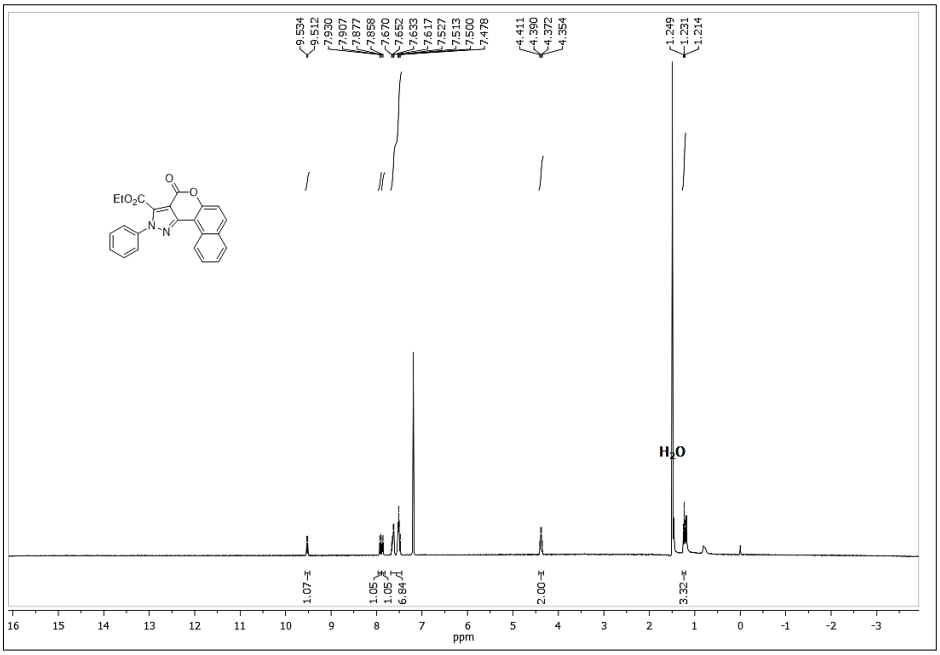


Figure 3.14 ^{1}H NMR spectrum of **3.3df**

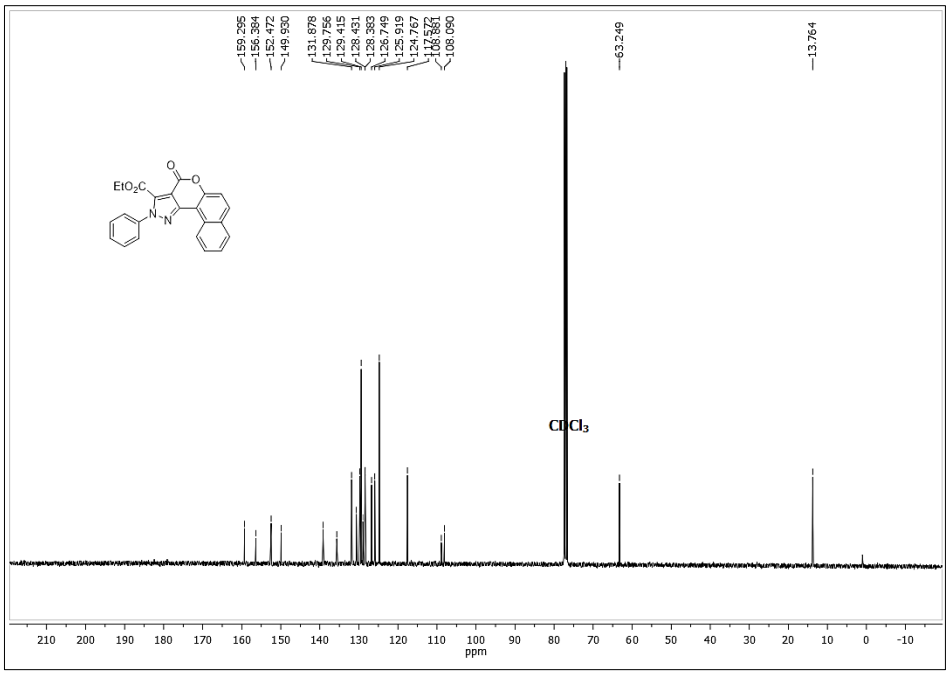


Figure 3.15 ^{13}C NMR spectrum of **3.3df**

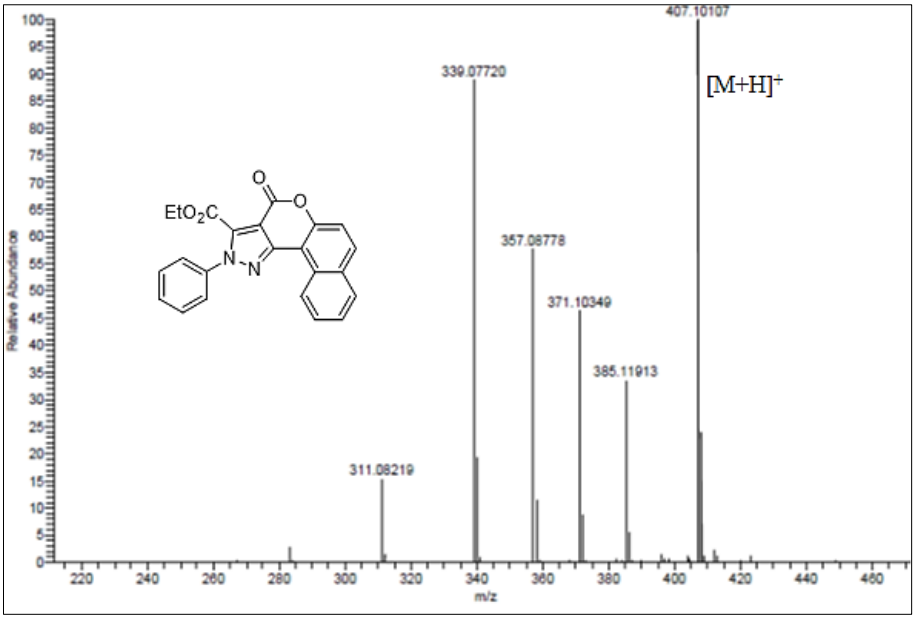


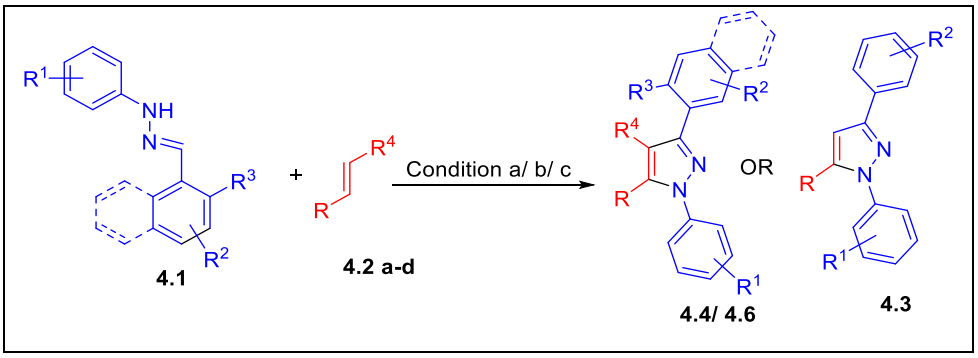
Figure 3.16 HRMS spectrum of **3.3df**

CHAPTER 4

AN INVESTIGATION ON THE REACTION OF ACTIVATED OLEFINS WITH ALDEHYDE HYDRAZONES: SYNTHESIS OF PYRAZOLES

Abstract

The reactivity of various activated alkenes toward the 1,3- dipolar cycloaddition with hydrazones has been studied. Nitroolefins, acrylates, acrylonitrile, and other electron-deficient alkenes have been explored in the reaction with aldehyde hydrazones to synthesize pyrazoles. A detailed optimization study was conducted to derive the best condition for annulation reactions of each olefin. Olefins with different electron withdrawing groups selectively reacted with N-aryl hydrazones under specific conditions.



4.1 INTRODUCTION

The pyrazole moiety is a prominent heterocyclic scaffold found in many natural and pharmacological compounds (Barroso et al. 2020; Faria et al. 2017; Khan et al. 2016; Poce et al.) Pyrazoles are widely used in materials chemistry applications as well as the food industry in addition to their medicinal applications (Chang et al. 2007; Maurya et al. 2017; Naskar et al. 2018; Orrego-Hernández et al. 2019; Sar et al. 2015; Yang et al. 2008). The development of effective pyrazole synthesis techniques has received much attention due to the widespread use of the pyrazole scaffold (Fustero et al. 2008, 2009; Kong et al. 2014; Zhu et al. 2015). The cyclocondensation of 1,3-dicarbonyl or α,β-unsaturated carbonyl compounds with hydrazines (Heller and Natarajan 2006; Marie Kissane and R. Maguire 2010; Wen et al. 2011) and intermolecular [3+2]-cycloadditions of diazo compounds with dipolarophiles such as alkenes and alkynes (Aggarwal et al. 2003; Chen et al. 2017a; Martina et al. 2019; Thombal and Lee 2018) are two common ways for the synthesis of pyrazole. The synthetic usefulness of these methods is limited by the need for strong reaction conditions and, in some cases, poor

regioselectivity. The 1, 3-dipolar cycloaddition method, on the other hand, has been widely used for regioselective and atom-economic pyrazole synthesis.

As discussed in the previous chapters, we have carried out a detailed investigation on the annulation of various N-aryl hydrazones across acetylenic esters which led to the direct synthesis of diversely substituted pyrazoles and chromenopyrazoles. Encouraged by these results, we speculated the possibility of annulating hydrazones across electron deficient alkenes, the typical Michael acceptors. Compared to acetylenic esters, more diversity is possible with such olefins which will eventually expand the scope of the strategy. Literature survey revealed that there are very few reports on the reaction of aldehyde hydrazones with activated olefins. The electrophilic olefins used for the annulation reactions include nitroalkenes, cyanoalkenes, enones, and α, β- unsaturated esters. **Figure 4.1** below shows the various activated olefins which can be used for the synthesis of pyrazoles by annulating with hydrazones.

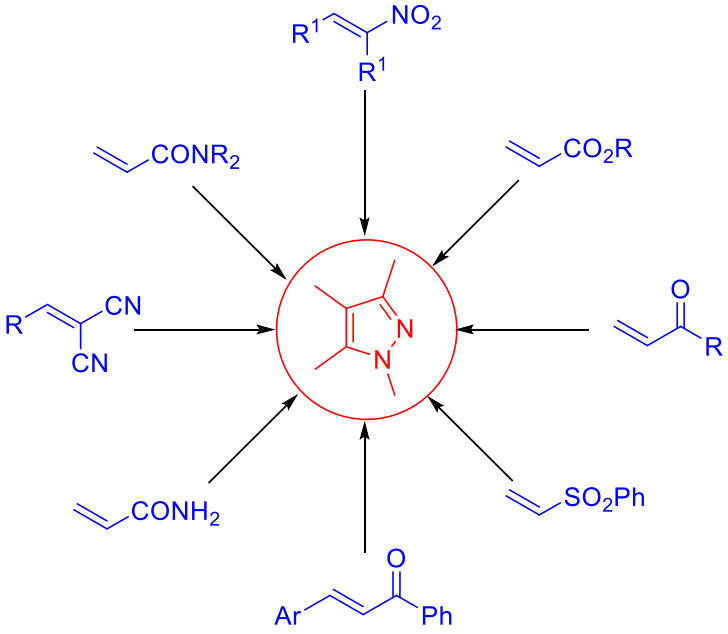
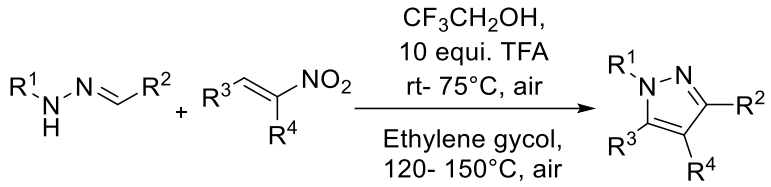


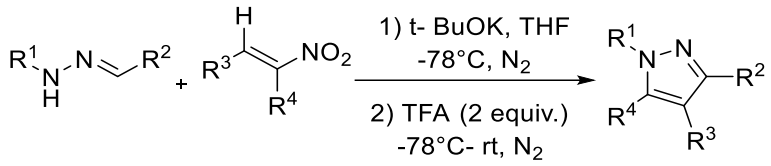
Figure 4.1 Activated olefins that can be used for pyrazole synthesis

Many heterocycles, notably pyrazoles, have been developed using hydrazones as a versatile starting materials (Lv et al. 2021). In an acid-promoted metal-free approach towards synthesizing substituted pyrazoles, we found that hydrazones effectively cyclize across activated alkynes under mild conditions to yield pyrazoles (Bhaskaran et al. 2020). Due to our continued interest in the chemistry of hydrazones, we were curious to explore the reactivity of aldehyde hydrazones with various Michael acceptors

such as nitroolefins, acrylates, vinyl ketones etc. Various diazo compounds are known to cyclize across dipolarophiles to yield diverse N-heterocycles. The reaction of electron-deficient N-aryl hydrazones with nitroolefins to generate 1,3,5-tri- and 1,3,4,5-tetrasubstituted pyrazoles was reported by Xiaohu Deng and co-workers (Deng and Mani 2006, 2008a; b). The reaction has a reversed, exclusive 1, 3, 4-regioselectivity when strong base like t-BuOK mediate it.

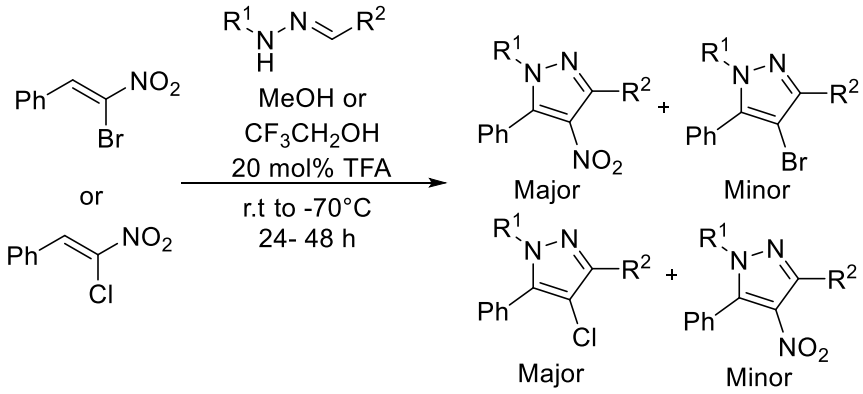


Scheme 4.1



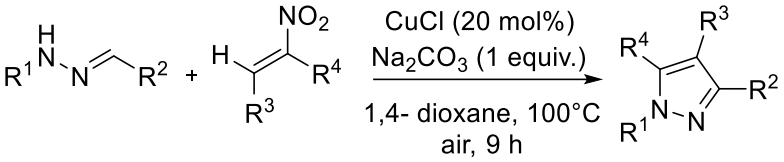
Scheme 4.2

The same group in 2014 reported the synthesis of 4-nitro-/4-chloro-tetrasubstituted pyrazoles using an acid-catalyzed cycloaddition reaction of hydrazones with β-bromo- or β-chloro / β-nitrostyrene (Deng et al. 2014).



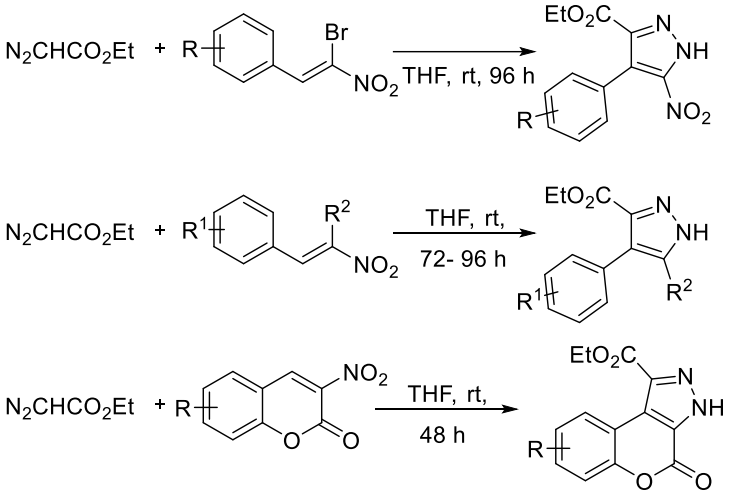
Scheme 4.3

Another approach for the synthesis of pyrazoles from the same substrates, in which Cu (I) catalyze the [3+2] cycloaddition, was reported by Chong Shi et al. in 2016 (Shi et al. 2016b).



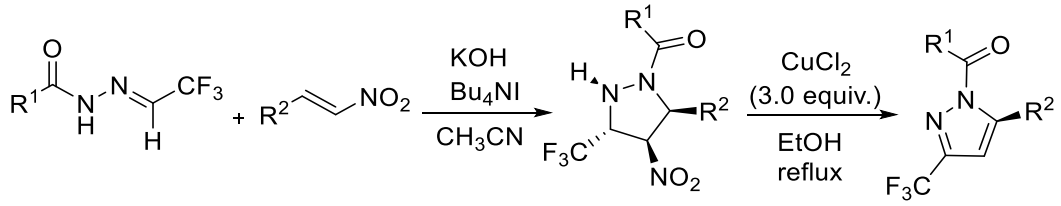
Scheme 4.4

A 1, 3- dipolar cycloaddition of ethyl diazoacetate with nitroalkenes was carried by Jian-Wu Xie and co-workers. Under favourable conditions, the one-pot reaction proceeds smoothly and yields pyrazole derivatives in moderate to good yields. They further synthesized the polycyclic benzopyrano[3,4-c]pyrazoles by incorporating a pyrazole heterocyclic unit into coumarins (Xie et al. 2009).



Scheme 4.5

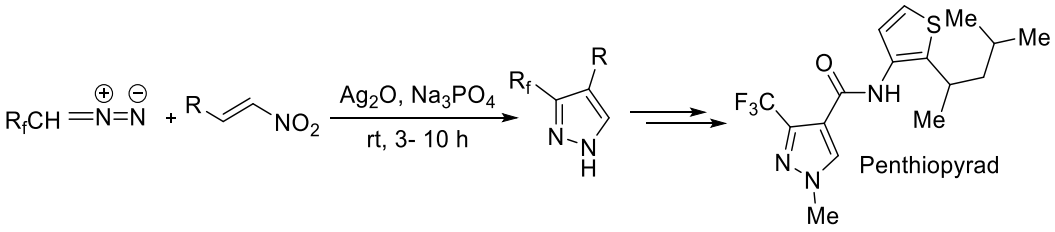
Xiansha peng et al. reported a base and PTC catalyzed [3+2] cycloaddition of N- acyl hydrazones and nitroolefins to synthesize biologically active trifluoromethylated pyrazolidines. The pyrazolidines formed were converted to pyrazoles by treating them with $CuCl_2$ (Peng et al. 2017).



Scheme 4.6

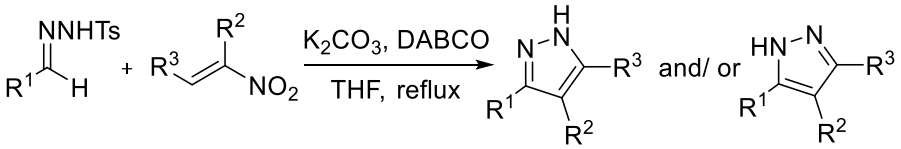
Zhen Chen and co-workers demonstrated the conversion of trifluoro and higher perfluoro diazomethane into 4-substituted 3-perfluoroalkyl pyrazoles by treating with nitroolefins. The nitro group acts as a traceless activating and directing functionality

for the transformation. The synthetic potential of this technique was revealed by the production of agrochemical fungicide penthiopyrad (Chen et al. 2017b).



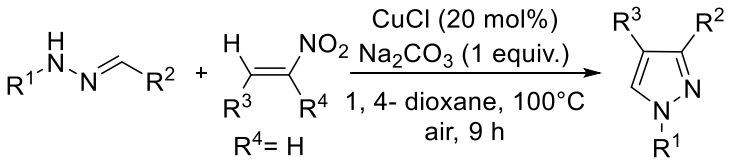
Scheme 4.7

A DABCO catalyzed cycloaddition of tosyl hydrazones with nitroalkenes was reported by Meng Tang et al. The reaction was based on the sequential Baylis Hillman/intramolecular cyclization mechanism. The products were isolated with high regioselectivity (Tang et al. 2013).



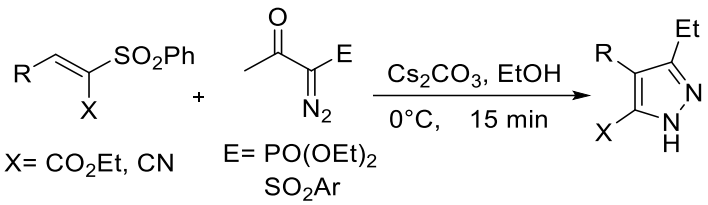
Scheme 4.8

The synthesis of 1,3,4-trisubstituted and 1,3,4,5-tetrasubstituted pyrazoles by cycloaddition of hydrazones and nitroolefins has been described using copper(I)-catalyzed regioselective technique. Under mild circumstances, this method shows an excellent application with a wide range of substrates (Shi et al. 2016a).



Scheme 4.9

The regioselective 1, 3-dipolar cycloaddition of diazomethylsulfone anion, produced in situ from α-diazo β-ketosulfone, with vinyl sulfone yields sulfonylpyrazoles. Phosphonylpyrazoles are formed when diazomethylphosphonate anion, produced from Bestmanne-Ohira reagent, reacts with vinyl sulfone. In these processes, the sulfonyl group of vinyl sulfone is chemoselectively eliminated (Kumar et al. 2014).



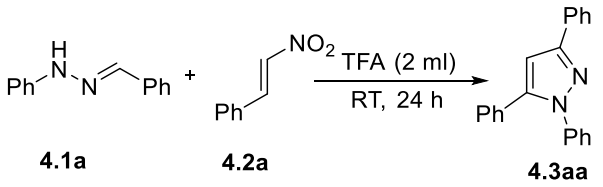
Scheme 4.10

As summarized above, the synthesis of pyrazoles from activated olefins and diazo compounds/hydrazones still attracts a lot of attention of synthetic chemists. In the light of our own previous results, it was worth to explore this area in detail and here we report our finding as a metal-free approach to synthesize N-aryl substituted pyrazoles from various activated alkenes and N-arylhydrazones.

4.2 PRESENT WORK

4.2.1 Synthesis of pyrazoles from *trans*-β-nitrostyrene

We commenced our investigations under the optimized reaction condition obtained for N-aryl hydrazones and acetylenic esters (Bhaskaran et al. 2020). 1-benzylidene-2-phenylhydrazine (**4.1a**) and *trans*-β-nitrostyrene (**4.2a**) was taken in a Schlenk tube, and TFA (2 ml) was added as the solvent. The reaction was allowed to stir at room temperature for 24 h. The product **4.3aa** was formed in 49% yield (**Table 4.1**, **entry 1**). The spectral analysis confirmed the structure of the isolated compound.



Scheme 4.11

The IR spectrum of 1, 3, 5-triphenyl-1H-pyrazole shows aromatic C-H stretching at 2920 cm^{-1} and 2856 cm^{-1}. The absorption peak at 1543 $cm^{-1}$and 1260 cm^{-1} corresponds to C-N stretching. ^{1}H NMR spectrum showed the aromatic proton in the pyrazole ring at δ 6.75 ppm as a singlet (**Figure 4.2**). All other aromatic protons of the compound resonates from 7.27 to 7.94 ppm. The structure was also confirmed using ^{13}C NMR (**Figure 4.3**) and mass spectrometry. HRMS results also supported the pyrazole structure (**Figure 4.4**).

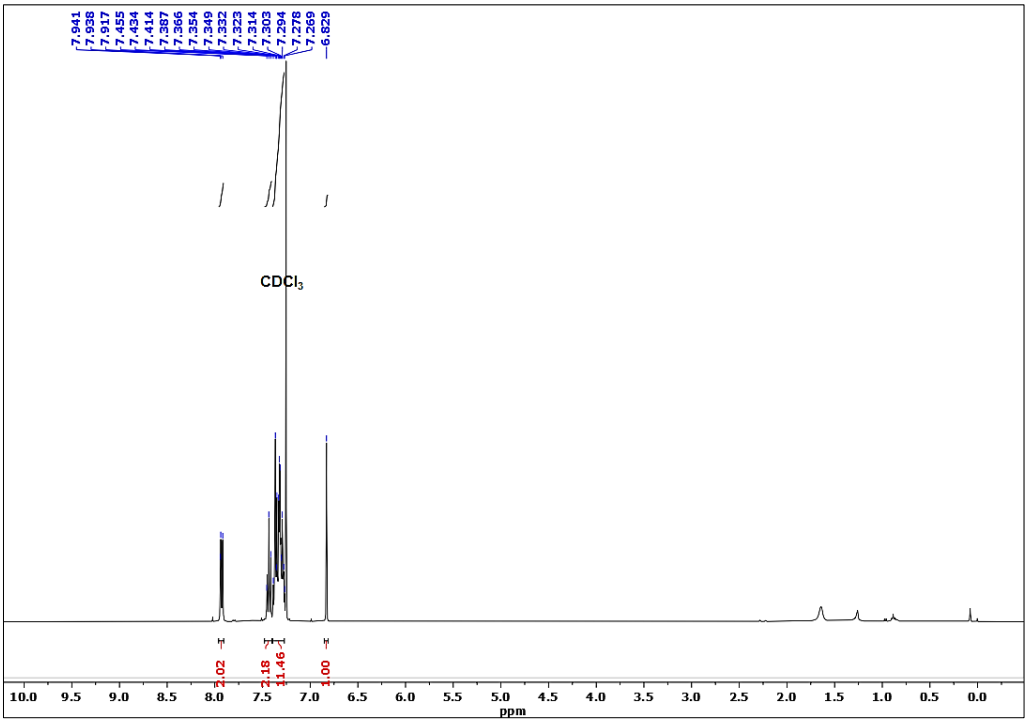


Figure 4.2 ^{1}H NMR spectrum of compound **4.3aa**

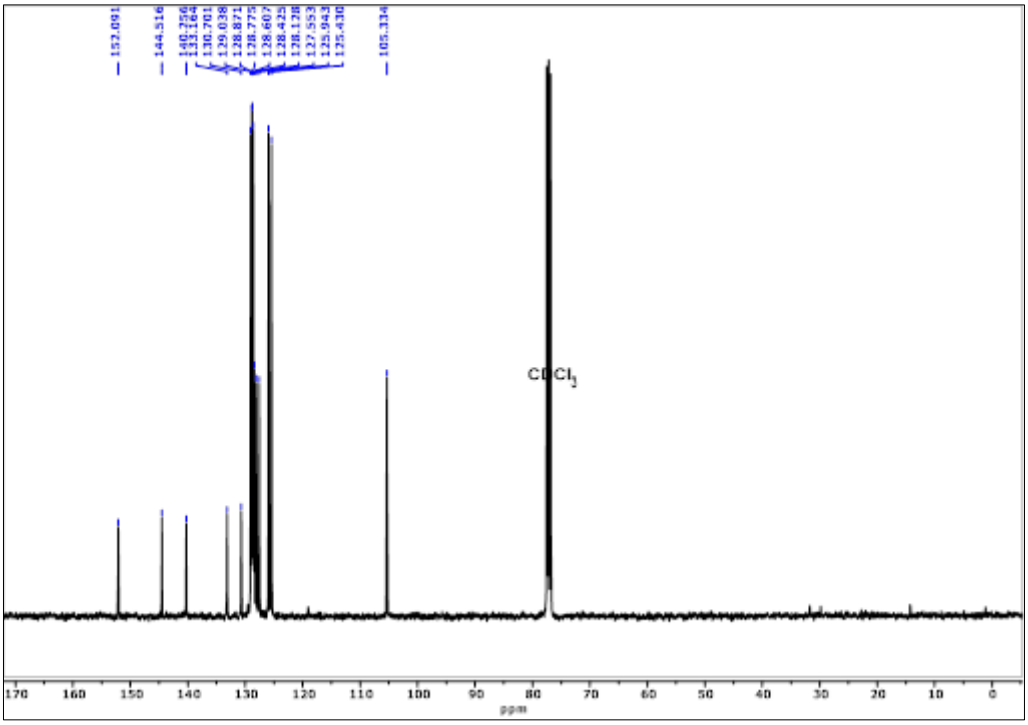


Figure 4.3 ^{13}C NMR spectrum of compound **4.3aa**

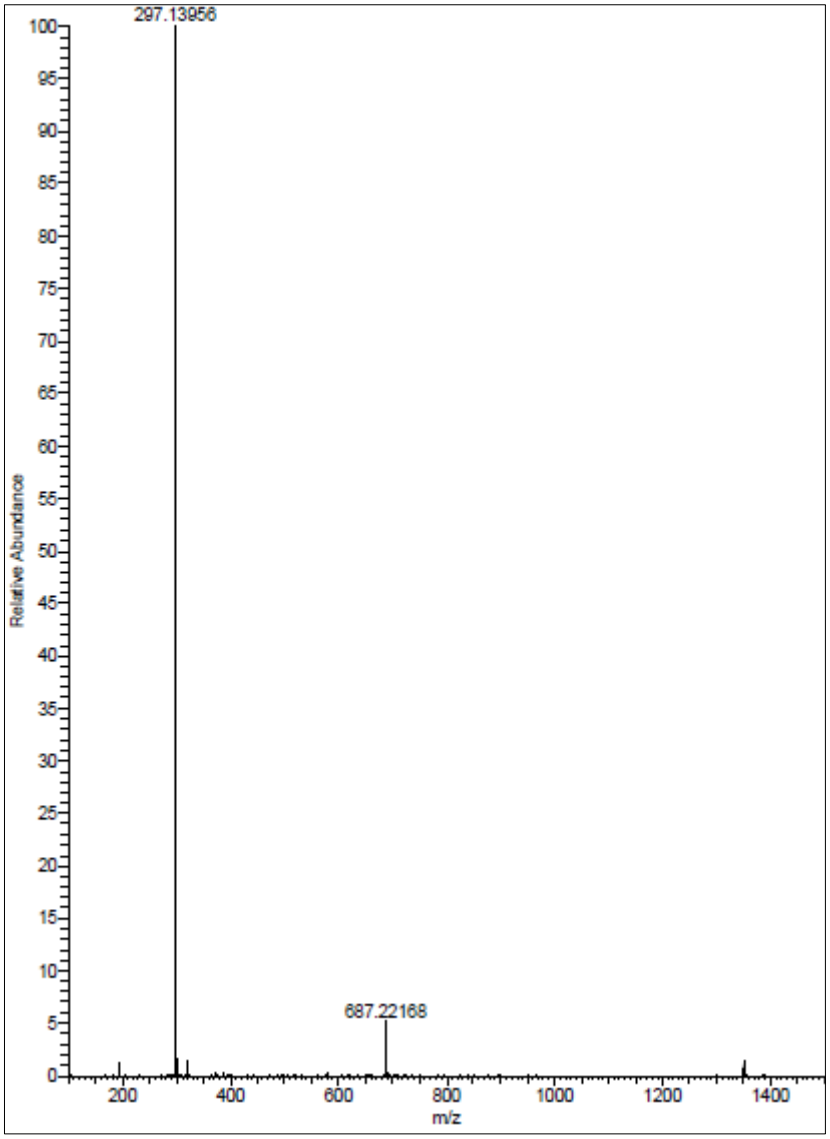
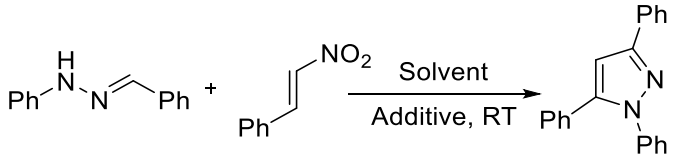


Figure 4.4 HRMS spectrum f compound **4.3aa**

4.2.1.1 Optimization of the reaction conditions and the substrate scope

After confirming the structure of the product **4.3aa** by the spectral techniques, a detailed optimization study was conducted to identify the best condition for the reaction by systematically varying the parameters such as stoichiometry of the reactants, additives, temperature, time duration, and solvent. In the absence of an acid additive, the reaction was not feasible. Shallow conversion was observed when catalytic (10 mol%) TFA was employed along with 1,2- DCE (1.5 ml). To improve the yield, we decided to perform the reaction by changing the stoichiometry of TFA. From the screening, it was quite evident that catalytic TFA and a large excess of TFA (as solvent) do not promote the

reaction. Among different solvents screened, 1, 2- DCE: TFA (3:1) afforded the best yield (**Table 4.1, entry 4**); increasing the reaction temperature did not improve the overall conversion. The time required for the maximum conversion of reactants to the product was monitored with TLC at regular intervals, and the reaction was complete within 6 h. Further, various acid additives such as p-toluene sulfonic acid, acetic acid, and pivalic acid were substituted in place of TFA (**Table 4.1, entries 9, 10 and 11**). The results obtained proved TFA as the best acid additive for the reaction.



4.1a **4.2a** **4.3aa**

Entry	**Solvent**	**Additive**	**Yield (%)[c]**
1	TFA[b]	----------	49
2	1,2- DCE	TFA (10 mol%)	Trace
3	1,2- DCE	TFA (1 equiv.)	30
4	1,2- DCE	TFA (14 equiv.)	75
5	Acetonitrile	TFA (14 equiv.)	50
6	DMSO	TFA (14 equiv.)	Trace
7	DME	TFA (14 equiv.)	38
8	Ethyl acetate	TFA (14 equiv.)	Trace
9	1,2- DCE	p- TsOH (14 equiv.)	Sluggish reaction
10	1,2- DCE	PivOH (14 equiv.)	Trace
11	1,2- DCE	AcOH (14 equiv.)	Trace

All reactions were carried out in 1.5 ml solvent in Schlenk tube. Reaction condition: a) 1-benzylidene-2-phenylhydrazine (0.5 mmol, 1 equiv.), *trans*-β-nitrostyrene (0.6 mmol, 1.2 equiv.)

b) TFA (2 ml)

c) Isolated yield after column chromatography.

Table 4.1 Optimization of the reaction conditions

Under the optimized conditions, we further checked the detailed substrate scope of the reaction varying the hydrazones (**Table 4.2**). Interestingly, electron-rich hydrazone (**4.1d**) and electron-deficient hydrazones (**4.1b**) actively participated in the reaction irrespective of the electronic nature to yield the final compounds **4.3da** and **4.3ba** respectively.

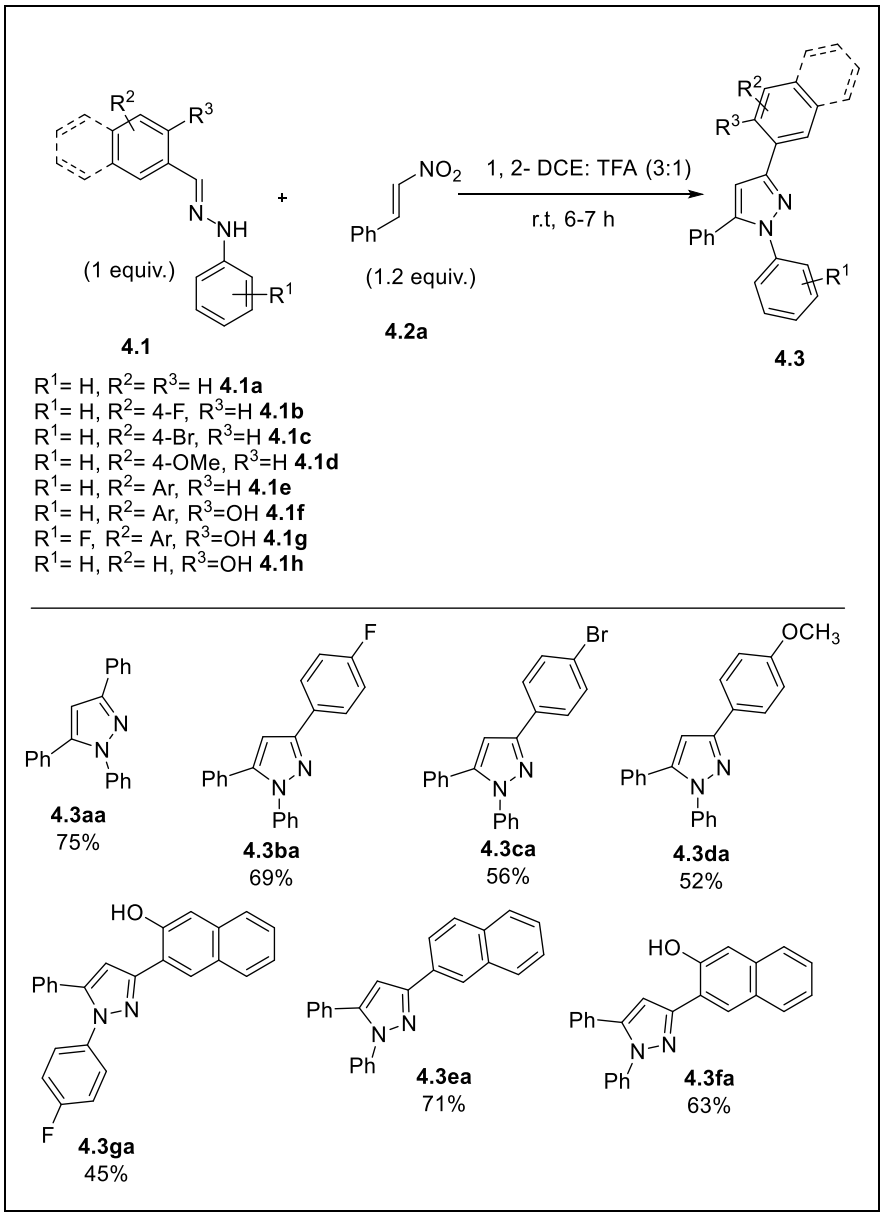
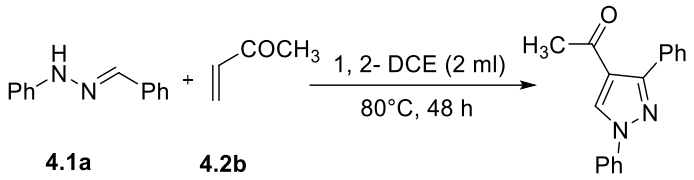


Table 4.2 Pyrazoles derivatives from N-aryl hydrazones and *trans*-β-nitrostyrene

4.2.2 Synthesis of pyrazoles from vinyl ketones

After exploring the substrate scope of the annulation of hydrazone across *trans*-β-nitrostyrene, we further proceeded with the reaction by changing the olefin counterpart. The olefins such as acrylates, methyl vinyl ketones, phenyl vinyl sulfones, and acrylamides were employed in the reaction to check the reactivity. An interesting reactivity was observed in the case of vinyl ketones. Contrary to the *trans*-β-nitrostyrenes reactivity, methyl vinyl ketone and hydrazone readily annulated in the absence of TFA. The annulation of hydrazone (**4.1a** 0.5 mmol, 1equiv.) to methyl vinyl ketone (**4.2b** 1.0 mmol, 2.0 equiv.) occurred in pure 1,2- DCE (2 ml) at 80 °C within 48 h, and resulted in the final product, pyrazole (**4.4ab**). The observation was quite interesting as this is the first report on the synthesis of pyrazole from vinyl ketones and N-aryl hydrazone. It was also noted that the annulation was not effective when pure TFA was used as the solvent while a complex TLC is observed when 1,2-DCE:TFA (1.5+0.5 ml) mixture was used as the solvent.



4.1a **4.2b** **4.4 ab**

Scheme 4.12

After 48 h of reaction, the product **4.4ab** was isolated by column chromatography. The IR absorption band at 1670 cm^{-1} confirms the presence of the carbonyl group in the compound. In the ^{1}H NMR spectrum, the unique singlet peak observed at δ = 8.4 ppm depicts the proton in the five-membered ring. All the aromatic protons are observed from 7.34 to 7.78 ppm. The three methyl protons appear as a singlet at δ = 2.38 ppm (**Figure 4.5**). The carbonyl carbon atom in the compound was observed at δ = 192.6 ppm. The methyl carbon atom shows a peak at δ = 29.5 ppm. All the aromatic carbon atoms present in the compound were also confirmed from the ^{13}C NMR spectra (**Figure 4.6**). In the mass spectrum of the compound, the MS (ESI) calculated for $C_{21}H_{17}N_2O$ $[M+H]^+$ was 263.1179, and the value found was 263.1234 (**Figure 4.7**).

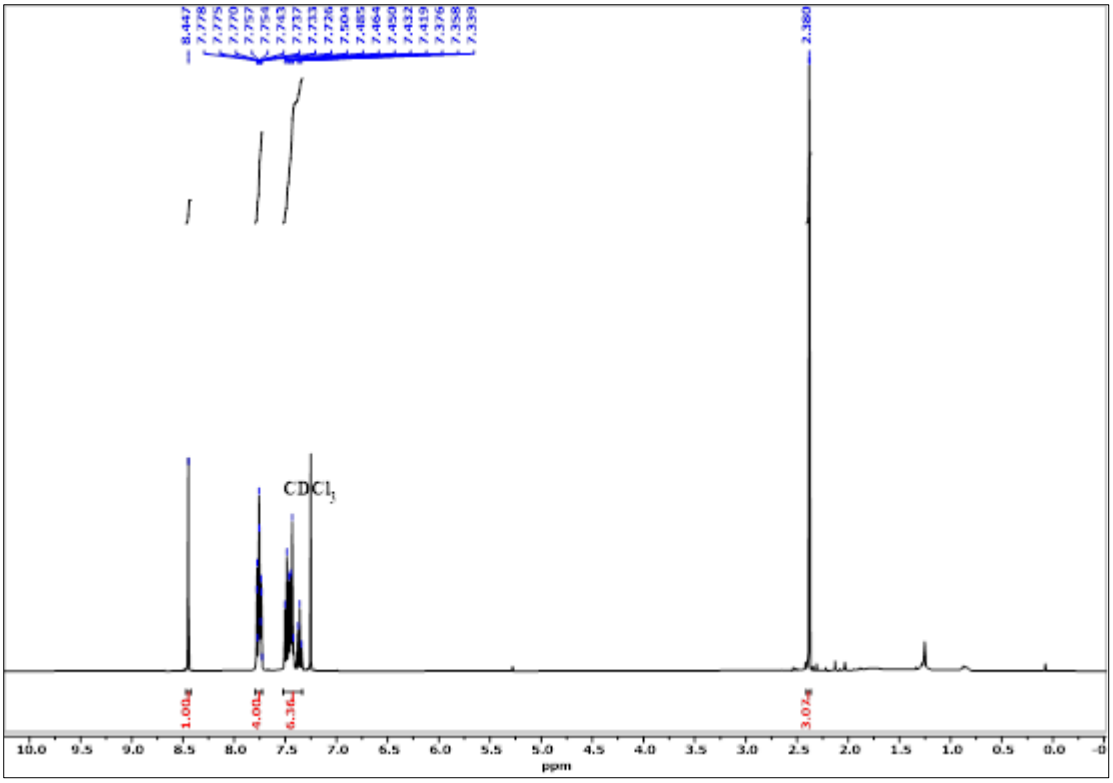


Figure 4.5 ^{1}H NMR spectrum of compound **4.4ab**

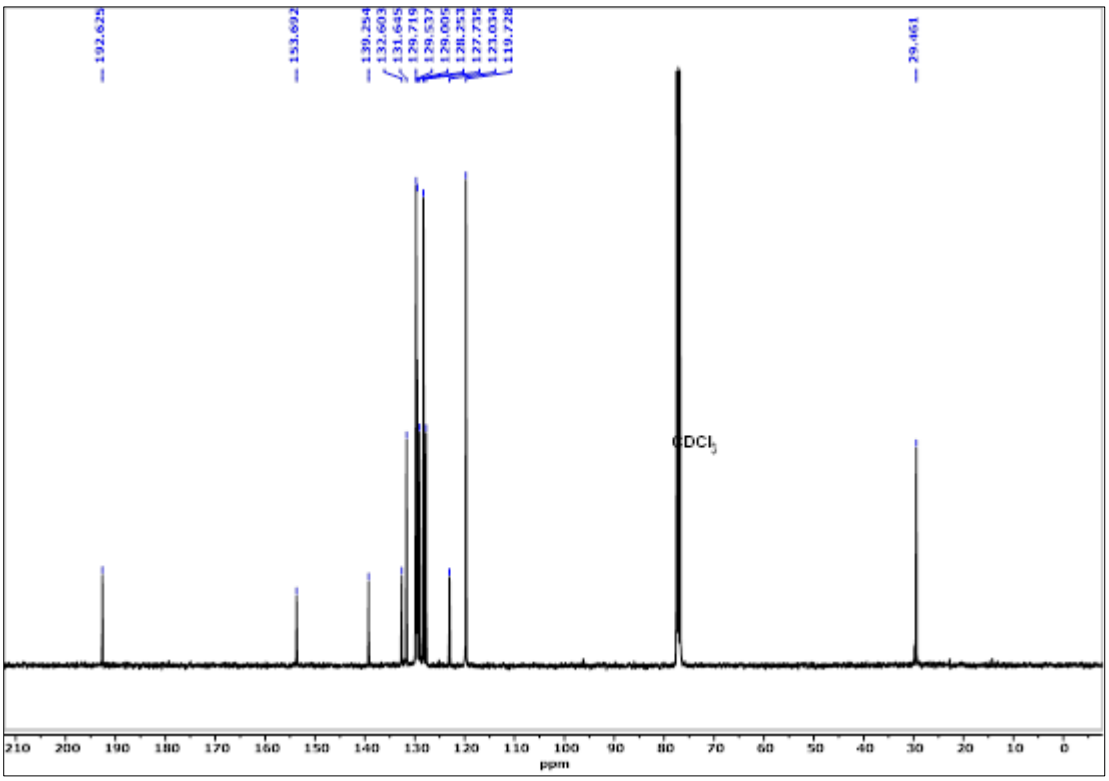


Figure 4.6 ^{13}C NMR spectrum of compound **4.4ab**

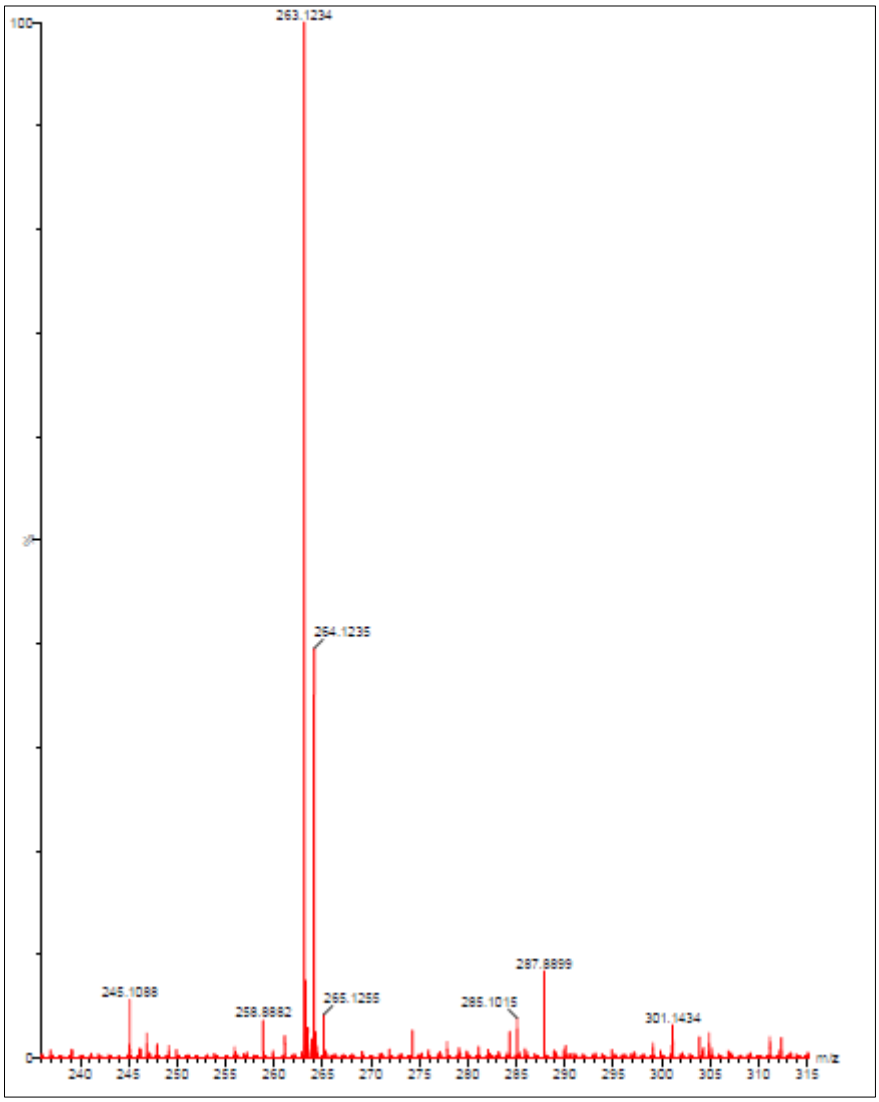


Figure 4.7 Mass Spectrum of compound **4.4ab**

N- aryl hydrazones with different electronic natures were incorporated to validate the substrate scope of the reaction. Hydrazones with electron withdrawing substitutions and electron donating substitutions actively annulated across methyl vinyl ketone to generate pyrazoles in moderately good yield (**4.4bb** & **4.4db**). Various pyrazole derivatives synthesized for the reaction of hydrazone and vinyl ketones are shown in **Table 4.3**.

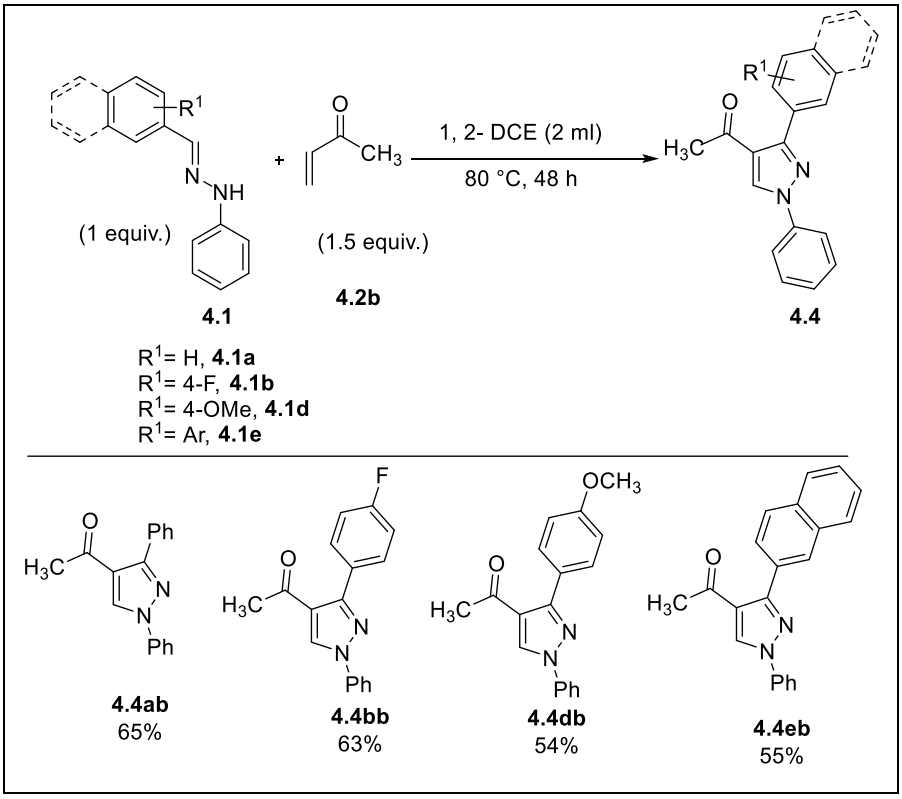
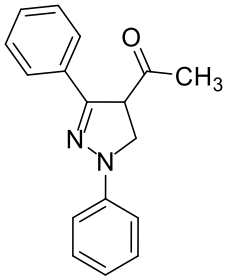


Table 4.3 Pyrazoles derivatives from N- aryl hydrazones and methyl vinyl ketone

In all these cases we observed the formation of trace amount of dihydropyrazole derivative as well. The formation of dihydropyrazole was confirmed from the proton NMR spectra. The ^{1}H NMR spectrum of 1-(1,3-diphenyl-4,5-dihydro-1H-pyrazol-4-yl)ethan-1-one (**4.5ab**) is shown in **Figure 4.8** The aromatic protons appears in the spectrum from 7.73 ppm- 6.90 ppm. The three protons present in the five- membered ring appears in the range of 4.40 ppm 4.03 ppm. The three methyl protons appear as a sharp singlet at 2.13 ppm. When we followed the progress of the reaction via TLC, it was found that the reaction mixture afforded a mixture of dihydropyrazole and pyrazole after 6h itself. However, the aromatization of the dihydropyrazole to pyrazole is a bit slow and after 48 hours of continuous heating, the dihydropyrazole almost completely got aromatized to pyrazole. Interestingly, keeping the reaction at room temperature for five continuous days (120 h) also afforded the dihydropyrazole almost exclusively.



4.5ab

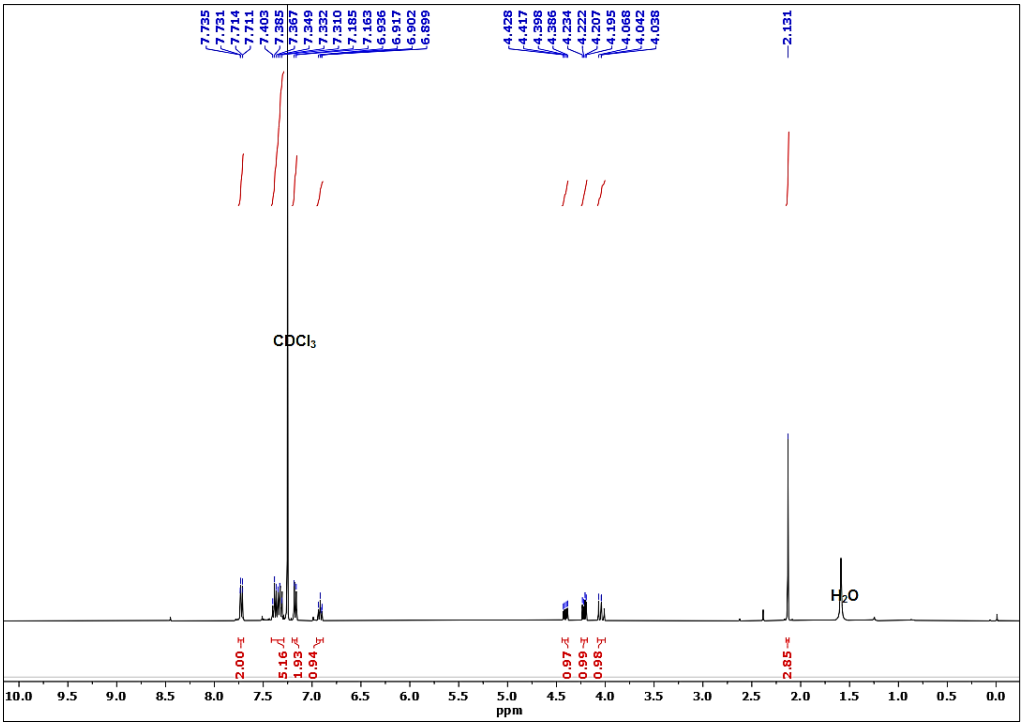
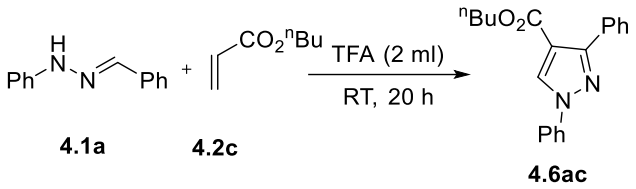


Figure 4.8 ^{1}H NMR spectrum of compound **4.5ab**

4.2.3 Synthesis of pyrazoles from α, β- unsaturated esters

Similar to nitrostyrene and vinyl ketones, we observed that hydrazones annulate across the α, β- unsaturated esters (acrylates), the typical Michael acceptor. N-butyl acrylate was chosen as the Michael acceptor. The product butyl-1,3-diphenyl-1H-pyrazole-4-carboxylate (**4.6ac**) was isolated in 85% yield when the reaction was carried out with 1-benzylidene-2-phenylhydrazine (**4.1a** 0.5 mmol, 1 equiv.) and n-butyl acrylate (**4.2c** 0.6 mmol, 1.2 equiv.) in pure TFA (2 ml) at room temperature for 20 h (**Scheme 4.13**).



Scheme 4.13

The white solid isolated from the reaction of 1-benzylidene-2-phenylhydrazine (0.5 mmol, 98 mg) with n-butyl acrylate (0.6 mmol, 76.8 mg) was characterized further using FTIR, NMR, and mass analysis. The carbonyl stretching frequency of the ester group in the compound was observed at 1680 cm^{-1}. In the ^{1}H NMR spectrum, the proton present in the five-membered ring resonates at $\delta = 8.43$ ppm as a sharp singlet. Aromatic protons are observed from the region of $\delta = 7.27$ ppm to $\delta = 7.79$ ppm. The two $–OCH_2$-protons resonate and appear as a quartet at $\delta = 4.16$ ppm with a coupling constant of 6.8 Hz. Aliphatic protons show signals from $\delta = 0.85$ ppm to $\delta = 1.61$ppm (**Figure 4.9**). The peak at $\delta = 162.1$ ppm in the ^{13}C NMR spectrum of the compound represents the carbonyl carbon atom of the ester group. All other signals observed in the spectrum were also in good agreement with the expected structure of the compound (**Figure 4.10**). Finally, the qualitative analysis was carried out by taking the mass spectrum of the compound. MS (ESI) calculated for $C_{20}H_{21}N_2O_2$ $[M+H]^+$ was 321.1598, and the obtained mass was 321.1647 (**Figure 4.11**).

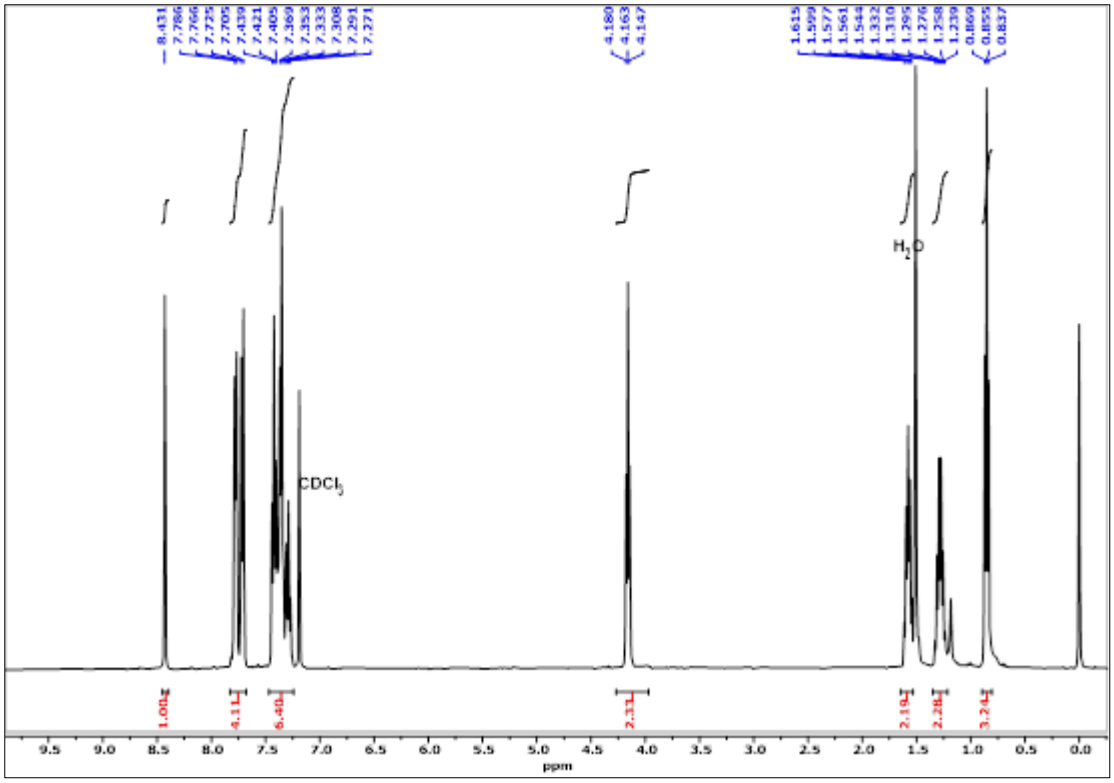


Figure 4.9 ^{1}H NMR spectrum of compound **4.6ac**

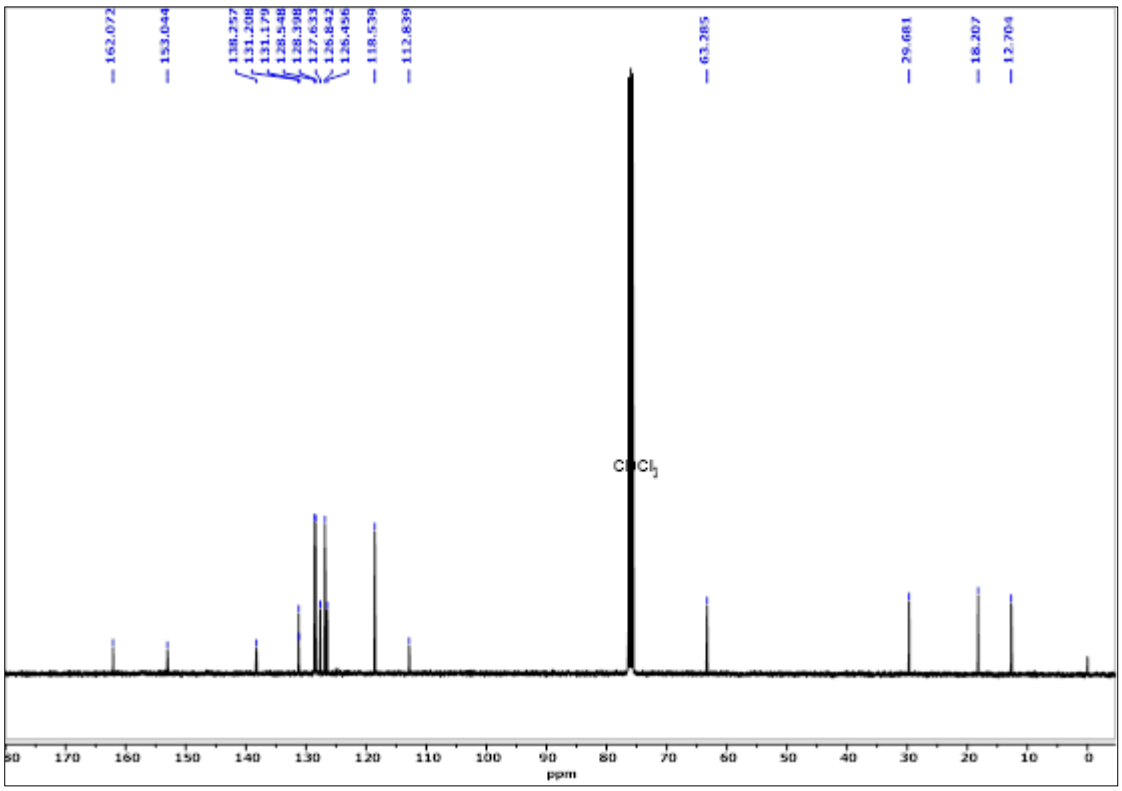


Figure 4.10 ^{13}C NMR spectrum of compound **4.6ac**

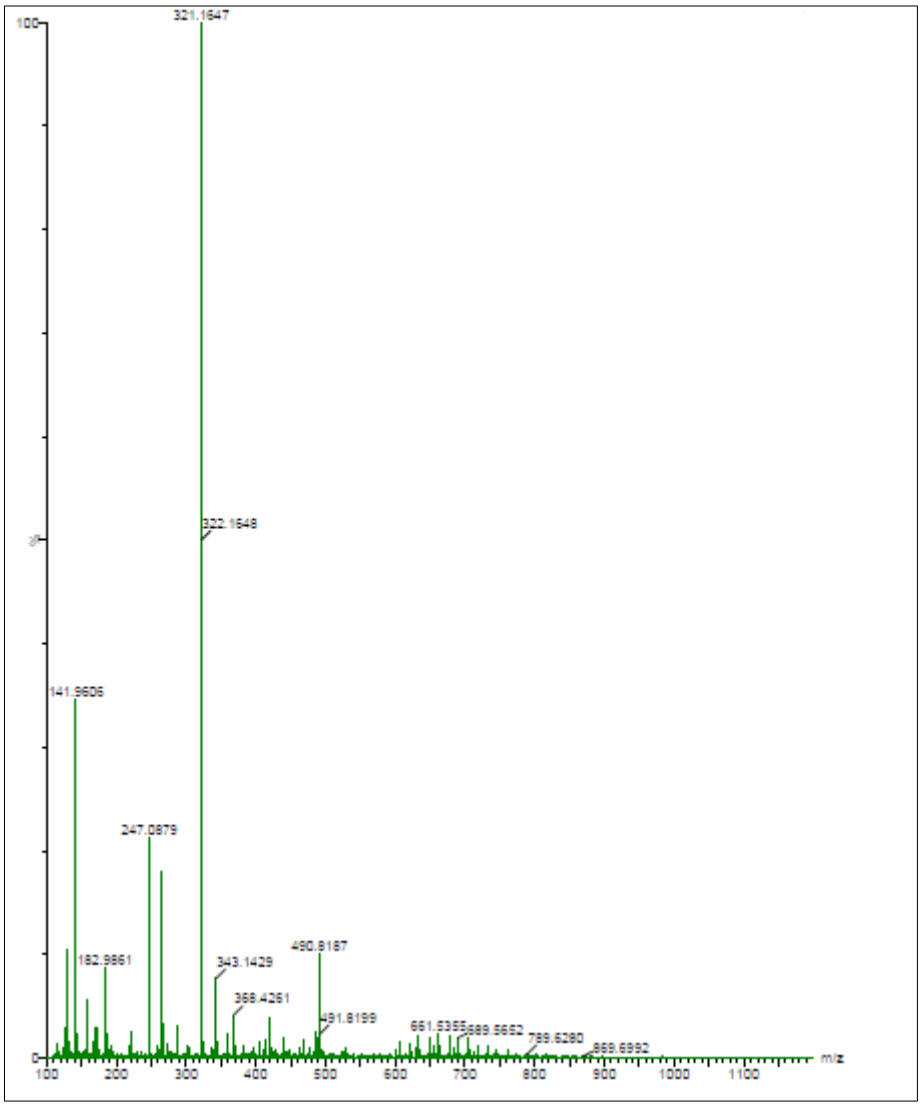


Figure 4.11 Mass spectrum of compound **4.6ac**

Finally, the structure of the derivative **4.6ac** was confirmed from the single crystal X-ray analysis. The ORTEP diagram of the same is shown in **Figure 4.12**.

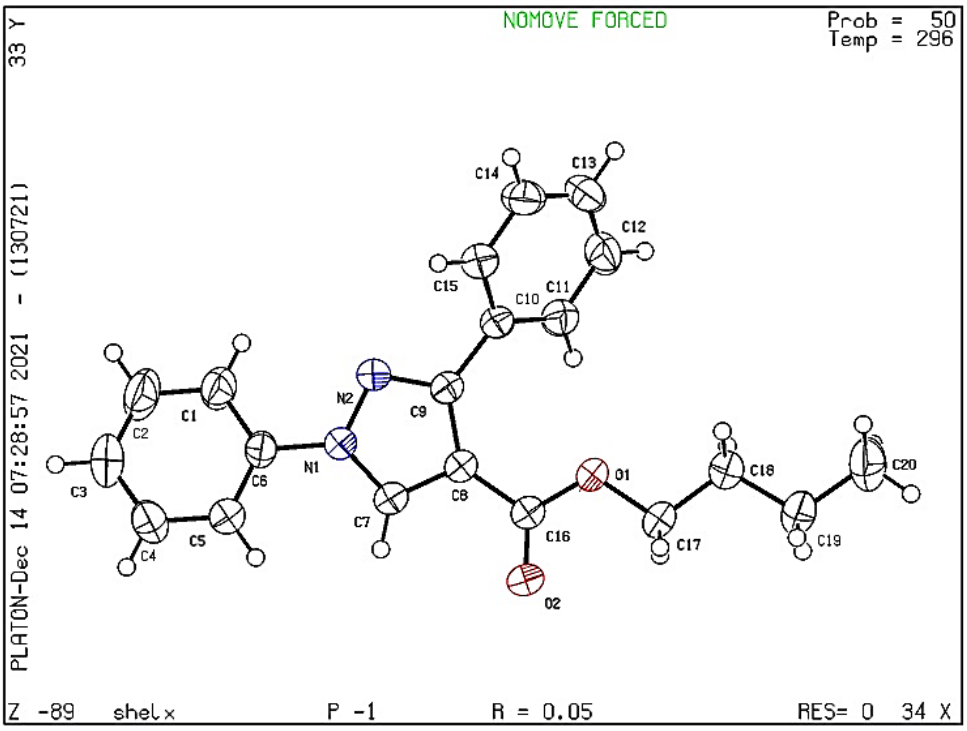
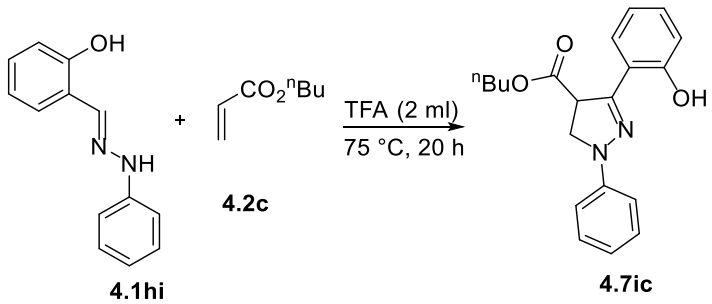


Figure 4.12 ORTEP diagram of **4.6ac** (CCDC No: 2130385)

Expecting the possibility of intramolecular lactonization of hydroxyl group to the ester group, the reaction between salicylaldehyde hydrazone (**4.1i**) and n-butyl acrylate (**4.2c**) was carried out at 75 °C. Contrary to the expectation, the resulted product was a dihydro derivative of pyrazole **4.7ic** (**Scheme 4.14**) without any aromatization (40%).



Scheme 4.14

Using FT-IR, NMR, and mass spectrometric techniques, the structure of the product **4.7ic** was confirmed. The carbonyl group of the ester shows an absorption band at 1731 cm^{-1}. The hydroxyl proton shows a peak at δ= 10.52 (s, 1H) ppm. All the aromatic protons appear in the region of δ= 6.89 ppm to δ= 7.37 ppm. Aliphatic protons in the butyl chain are present from δ= 0.85 ppm to δ= 1.62 ppm. The methoxy protons and the three protons present in the five membered ring show the peaks in the region of δ=

3.53 ppm to δ= 4.21 ppm (**Figure 4.13**). In the ^{13}C NMR spectrum of the compound, the six sp^3 carbon atoms correspond to the peaks in the up field from δ= 13.7 ppm to δ= 65.9 ppm. The carbonyl carbon atom shows a peak at δ= 171.2 ppm. All the aromatic carbon atoms are present in the spectrum from δ= 113.2 ppm to δ=157.2 ppm (**Figure 4.14**). The mass of the compound was found to be 339.1731$(M+H)^+$ in the spectrum, which was found to be in agreement with the calculated value 330.1703 (**Figure 4.15**).

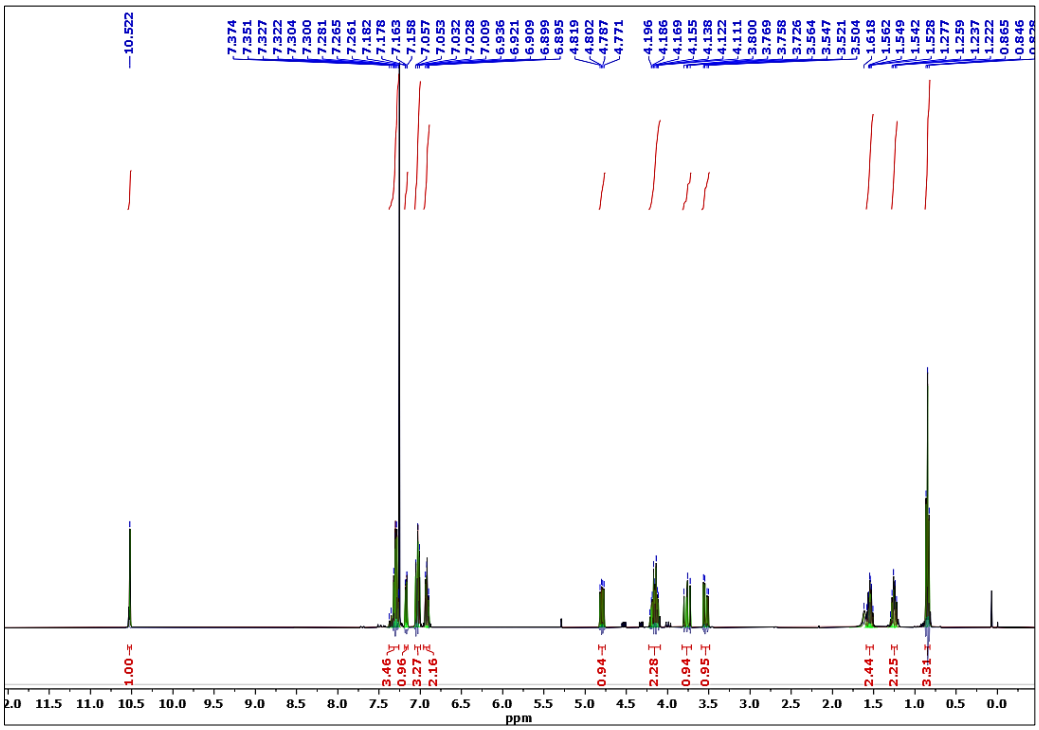


Figure 4.13 ^1H NMR spectrum of compound **4.7ic**

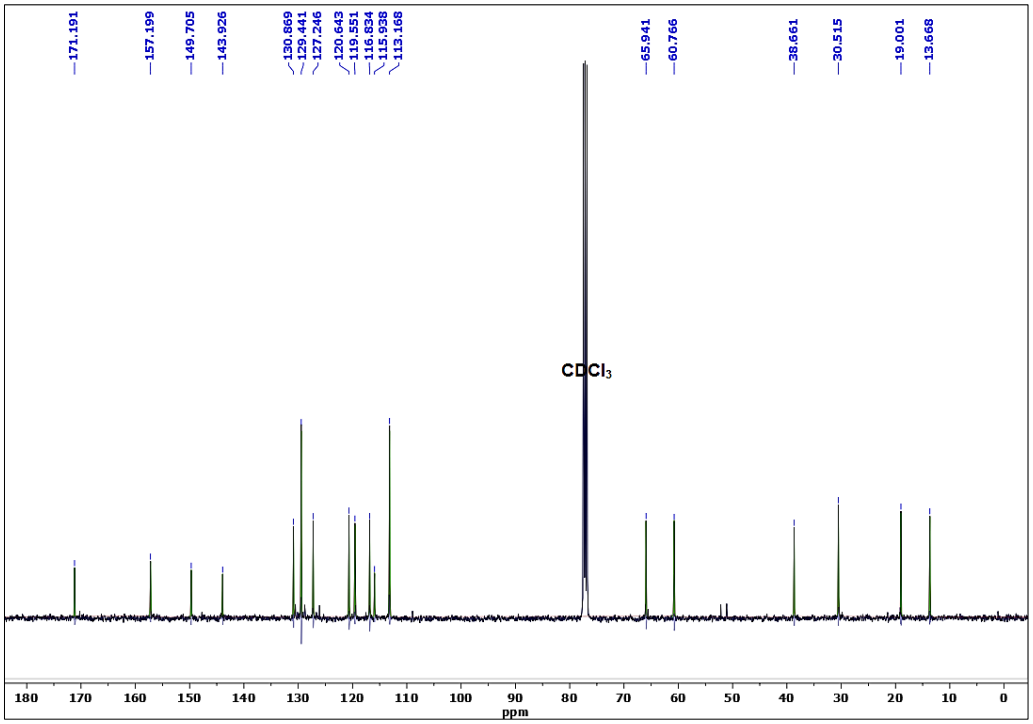


Figure 4.14 ^{13}C NMR spectrum of compound **4.7ic**

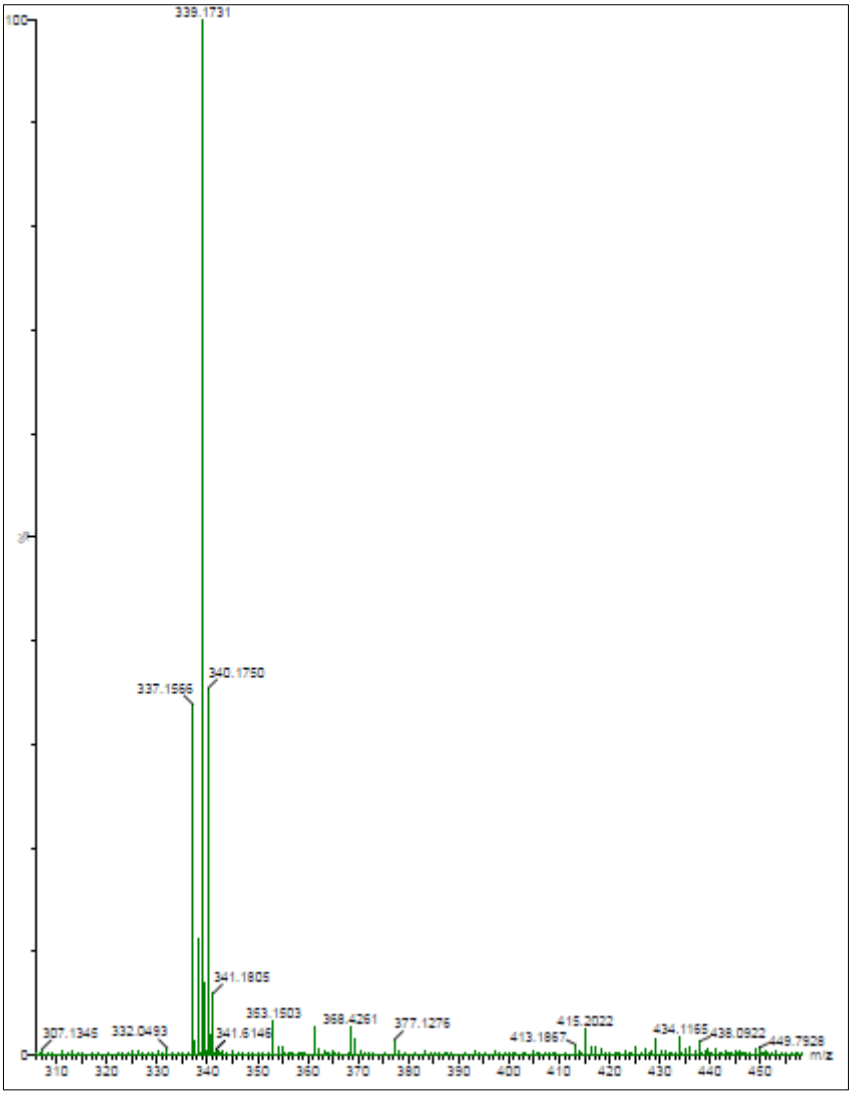
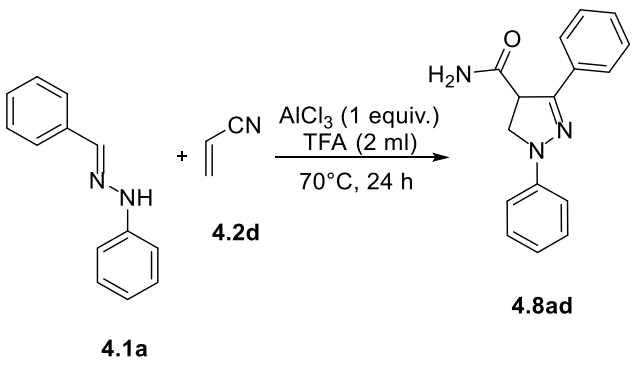


Figure 4.15 Mass spectrum of compound **4.7ic**

Interestingly, when acrylonitrile (**4.2d**) was employed in place of acrylate, the annulation was successful only in presence of the Lewis acid $AlCl_3$ (**Scheme 4.15**) and the dihydro derivative, 1,3-diphenyl-4,5-dihydro-1H-pyrazole-4-carboxamide (**4.8ad**) was formed exclusively (53 %).



Scheme 4.15

The structural characterization of the compound was carried out by taking FT-IR, ^{1}H NMR, ^{13}C NMR and mass spectrum (**Figures 4.16, 4.17** and **4.18**).

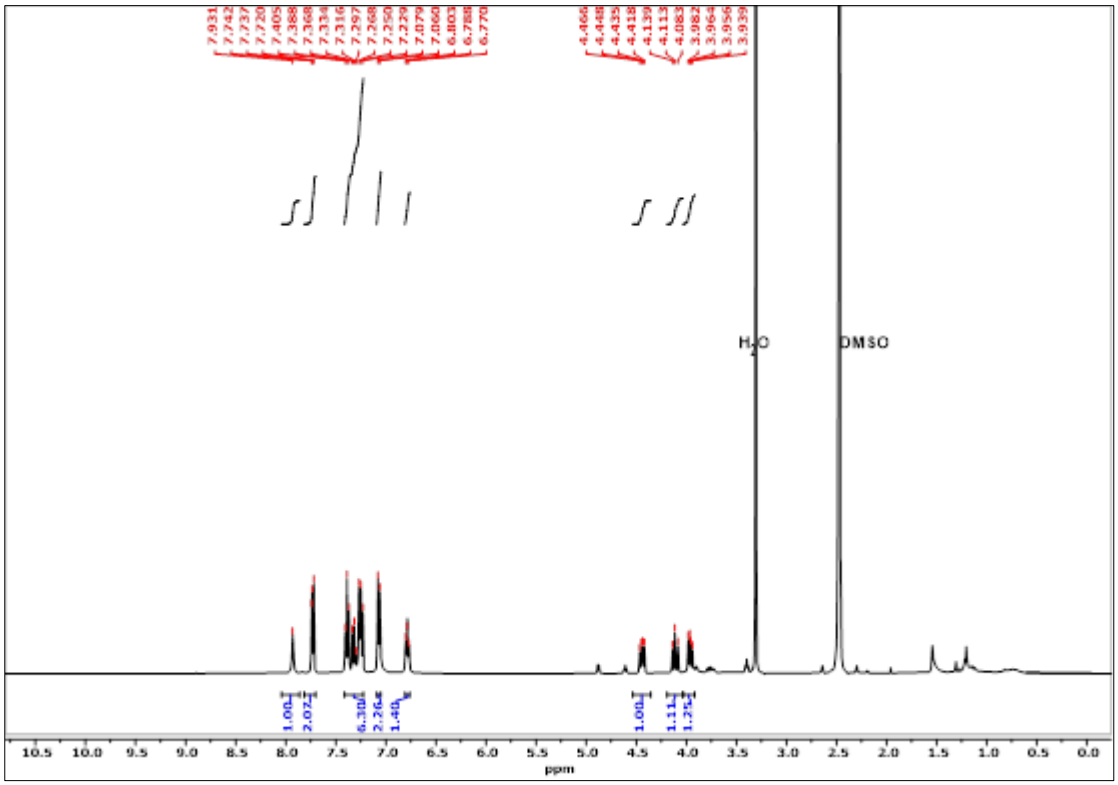


Figure 4.16 ^{1}H NMR spectrum of compound **4.8ad**

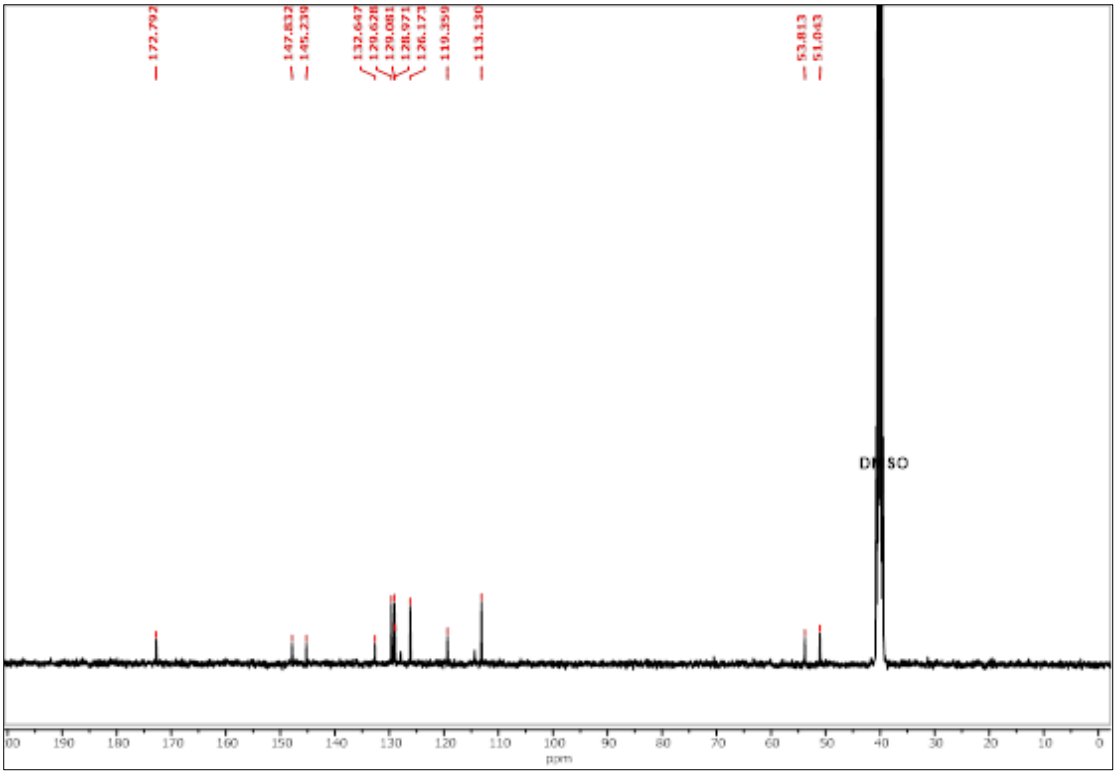


Figure 4.17 ^{13}C NMR spectrum of compound **4.8ad**

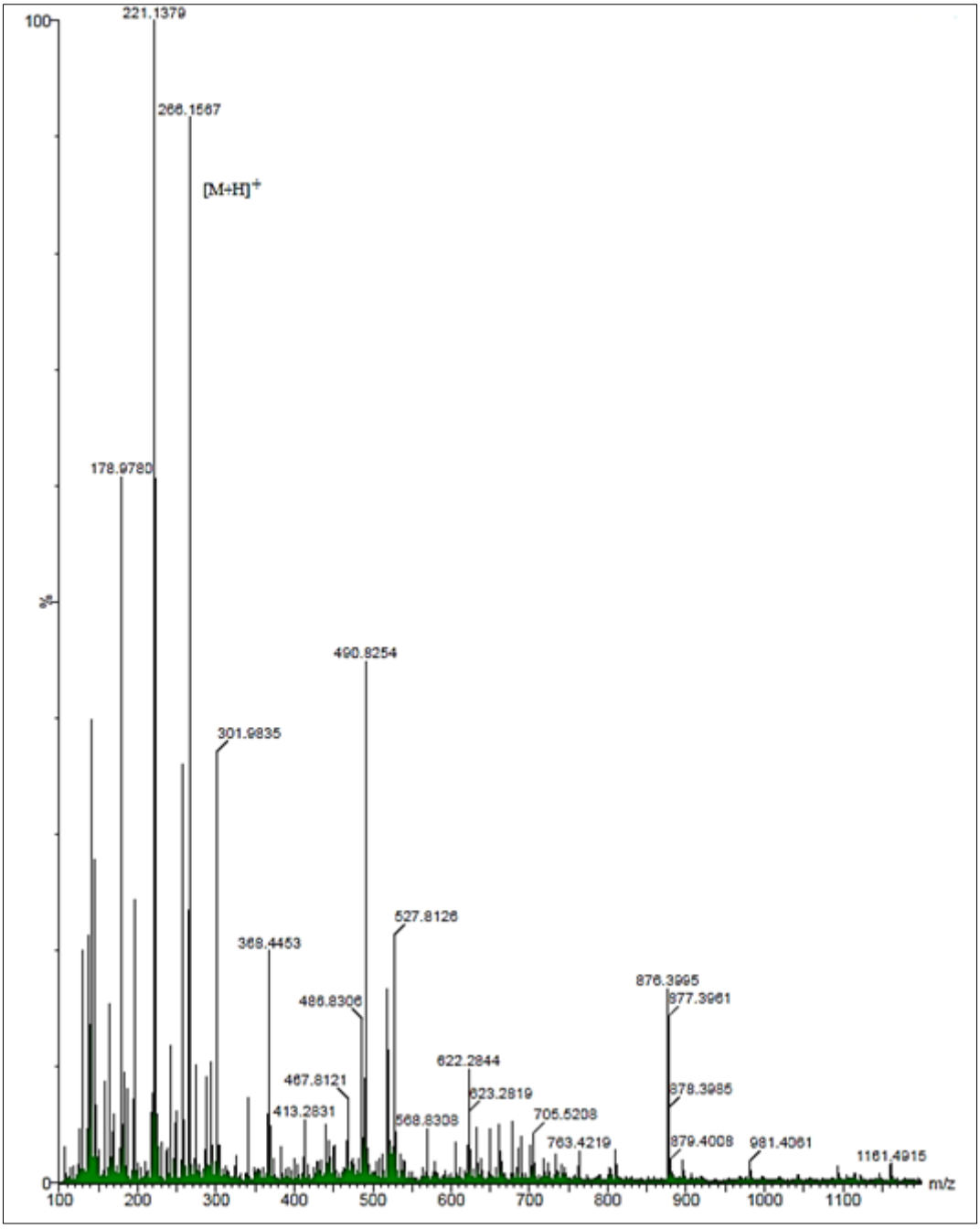
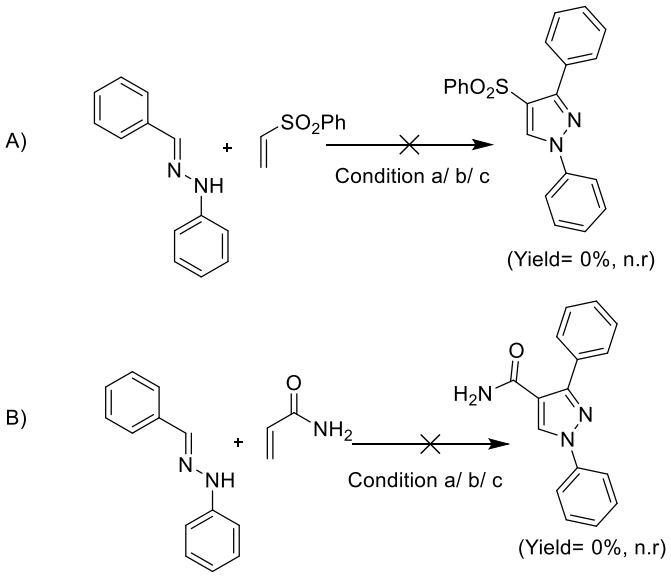


Figure 4.18 Mass spectrum of compound **4.8ad**

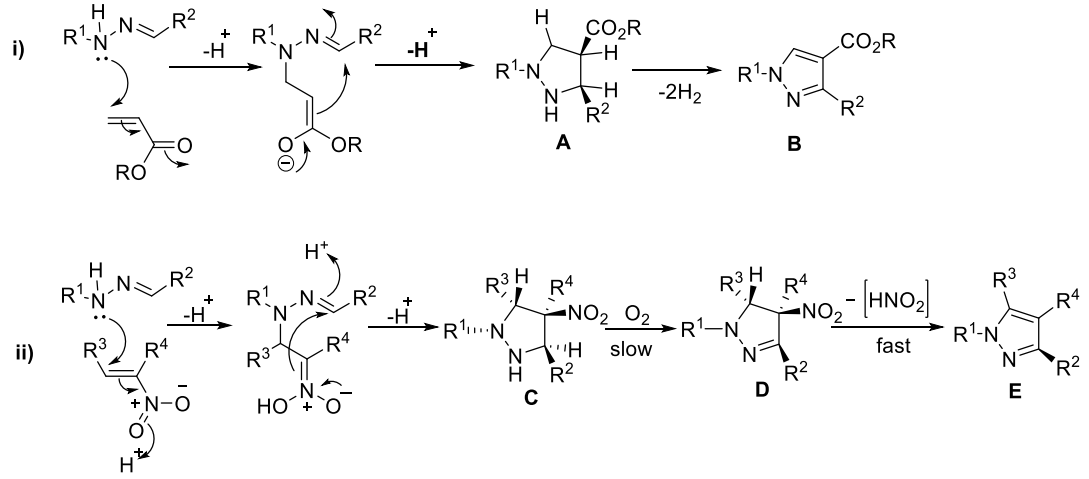
However, activated olefins such as phenyl vinyl sulfones and acrylamides failed to react with hydrazone in all the optimized conditions as listed in the **Scheme 4.16**.



a) Hydrazone (1 equiv.), Alkene (1.2 equiv.), 1,2- DCE:TFA (3:1), rt/ 6-7h.
b) Hydrazone (1 equiv.), Alkene (1.5 equiv.), 1,2-DCE (2 ml), 80°C/ 48h
c) Hydrazone (1 equiv.), Alkene (1.2 equiv.), TFA (2 ml), rt/ 20 h.
nr = no reaction

Scheme 4.16

Based on the observed reactivities of various activated olefins and also based on previous literature report (Deng and Mani 2008c), the possible mechanism for the annulation reaction is shown in **Scheme 4.17 (i)**.



Scheme 4.17

Initially, the nucleophilic addition of the hydrazone to the activated olefin takes place to afford a stabilized carbanion (due to the -NO_2/-COX group) which eventually cyclize to form the diversely functionalized dihydro pyrazole derivatives. Subsequent dehydrogenation of the dihydro pyrazole yield the final pyrazole. In the case of

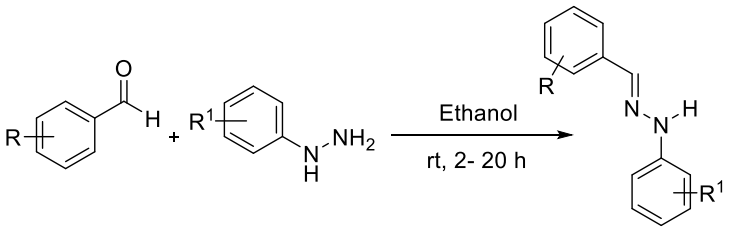
nitroolefins, the intermediate **C** formed was subjected to HNO_2 elimination followed by oxidation to form pyrazole product (**Scheme 4.17 (ii)**).

4.3 Conclusions

- A cycloaddition strategy towards the synthesis of substituted pyrazoles from N-aryl hydrazones and activated olefins was developed.
- The key highlights of the methodology include relatively mild and metal-free conditions (except acrylonitrile) with readily available substrates.
- A wide range of functional group tolerance was observed with reference to both hydrazones and olefins (Compounds **4.3aa** to **4.8ad**).
- All the final compounds synthesized were isolated and characterized by FT-IR, ^{1}H NMR, ^{13}C NMR, Mass Spectrometry and SCXRD.
- Olefins with various electron-withdrawing substitutions exclusively reacted with hydrazones in specific conditions.
- *trans*-β-nitrostyrene and alkyl acrylates readily yielded pyrazoles in acidic medium at room temperature.
- Methyl vinyl ketones afforded the pyrazole in the absence of TFA at 80 °C.
- Hydrazone when reacted with acrylonitrile yielded an amide derivative, 1,3-diphenyl-4,5-dihydro-1H-pyrazole-4-carboxamide (**4.8ad**) as the final product.
- The structure of the pyrazole formed was unambiguously confirmed by performing the single crystal X- ray diffraction analysis for the derivative **4.6ac**.

4.4 Experimental section

4.4.1 General procedure for the synthesis of hydrazones

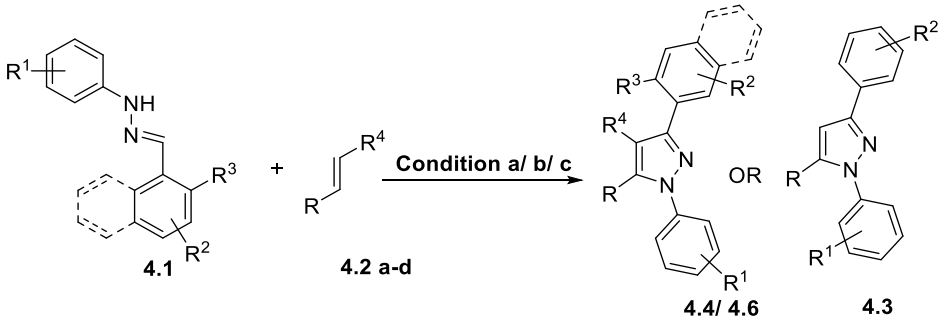


Scheme 4.18

In ethanol, phenyl hydrazine (1 equiv.) was stirred in a round bottom flask at room temperature. To the stirring solution, the corresponding aldehyde (1 equiv.) was added

(solid aldehyde was added portion-wise and liquid aldehyde dropwise) and stirred the mixture for about 8-20 hours (depending on the electronic nature of aldehydes). Progress of the reaction was monitored by checking TLC. After the completion of the reaction, the mixture was poured into ice-cold water. The precipitate formed was filtered off and washed with ice cold water followed by a pet ether. The solid mass obtained was dissolved in dichloromethane, dried using Na_2SO_4. The solvent was evaporated under the vacuum, and the product obtained was used for all other reactions.

4.4.2 General procedure for the synthesis of pyrazole derivatives



Scheme 4.19

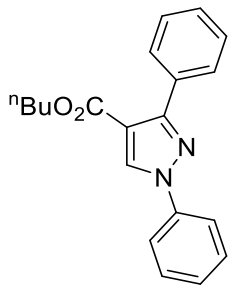
Condition a) Hydrazone (0.5 mmol, 1equiv.) was taken in an oven-dried Schlenk tube equipped with a magnetic stirrer. To this, *trans*-β-nitrostyrene (0.6 mmol, 1.2 equiv.) was added, followed by 1.5 ml 1, 2- DCE (solvent). To this mixture, 14 equiv. of TFA was added using a syringe. The reaction was kept at room temperature for about 6-7 h with continuous monitoring by checking TLC. After the reaction, the reaction mixture was then washed with saturated $NaHCO_3$ solution, and the organic layer was extracted in ethyl acetate. The ethyl acetate layer was finally washed with brine solution and the organic layer is dried over anhydrous sodium sulphate and evaporated under reduced pressure. The residue was purified by silica gel column chromatography using pet ether-ethyl acetate as eluent.

Condition b) Hydrazone (0.5 mmol, 1equiv.) was taken in an oven-dried Schlenk tube equipped with a magnetic stirrer. To this, Methyl vinyl ketone (1.0 mmol, 2 equiv.) was added, followed by 2 ml 1, 2- DCE (solvent). The reaction mixture was heated at 80°C for 48 h, with continuous monitoring by checking TLC. After the reaction, the solvent was evaporated, and the residue was purified by silica gel column chromatography using pet ether-ethyl acetate as eluent.

Condition c) Hydrazone (0.5 mmol, 1equiv.) was taken in an oven-dried Schlenk tube equipped with a magnetic stirrer. To this, alkyl acrylate (0.6 mmol, 1.2 equiv.) was added, followed by 2 ml TFA (solvent). The reaction was kept at room temperature for about 20 h with continuous monitoring by checking TLC. The reaction mixture was then washed with saturated $NaHCO_3$ solution, and the organic layer was extracted in ethyl acetate. The ethyl acetate layer was finally washed with brine solution, dried over anhydrous sodium sulphate and evaporated under reduced pressure. The residue was purified using pet ether- ethyl acetate as eluent by silica gel column chromatography.

4.4.3 ^{1}H NMR, ^{13}C NMR, and HRMS spectral data and images of pyrazole derivatives

butyl 1,3-diphenyl-1*H*-pyrazole-4-carboxylate (4.6ac): Following the general procedure (condition c), the reaction between 1-benzylidene-2-phenylhydrazine (0.5 mmol, 98 mg) with n-butyl acrylate (0.6 mmol, 76.8 mg, 85.9 µl) yielded the desired product butyl 1,3-diphenyl-1*H*-pyrazole-4-carboxylate as a white solid in 85% yield (136 mg).



Chemical Formula: $C_{20}H_{20}N_2O_2$

Melting point 87- 89°C.

FT-IR (ATR): ν_{max}= 3127, 2957, 1680, 1526, 1278, 1226, 1142 cm^{-1}

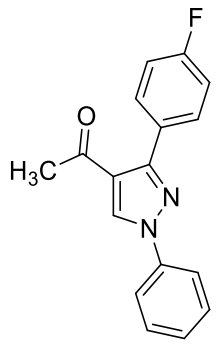
^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.43 (s, 1H), 7.79- 7.71 (m, 4H), 7.44 –7.27 (m, 6H), 4.16 (q, *J* = 6.8 Hz, 2H), 1.61- 1.54 (m, 2H), 1.33- 1.24 (m, 2H), 0.85 (t, *J* = 5.6 Hz, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ = 162.1, 153.0, 138.3, 131.2, 131.17, 128.5 (2C), 128.4 (2C), 127.6, 126.8 (2C), 126.4, 118.5 (2C), 112.8, 63.3, 29.7, 18.2, 12.7 ppm

MS (ESI) calcd for $C_{20}H_{21}N_2O_2$ $[M+H]^+$ 321.1598 found 321.1647.

1-(3-(4-fluorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)ethan-1-one (4.4bb): Following the general procedure (condition b), the reaction between 1-(4-fluorobenzylidene)-2-

phenylhydrazine (0.5 mmol, 107 mg) with Methyl vinyl ketone (1.0 mmol, 70.0 mg, 83.23 µl) yielded the desired product 1-(3-(4-fluorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)ethan-1-one as a white solid in 45% yield (63.0 mg).



Chemical Formula: $C_{17}H_{13}FN_2O$

Melting point 117-119°C.

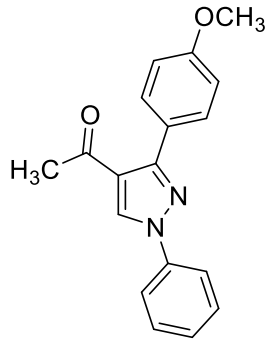
FT-IR (ATR): ν_{max}= 3067, 2926, 1717, 1672, 1516, 1449, 1223 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.43 (s, 1H), 7.80- 7.74 (m, 4H), 7.51 –7.47 (m, 2H), 7.38- 7.35 (m, 1H), 7.14- 7.09 (m, 2H), 2.43 (s, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ = 192.2, 164.6, 162.1, 152.7, 131.98, 131.5, 131.4, 129.7 (2C), 128.6, 127.8, 122.5, 119.7 (2C), 115.3, 115.1, 29.4 ppm

MS (ESI) calcd for $C_{17}H_{14}FN_2O$ $[M+H]^+$ 281.1085 found 281.1141.

1-(3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)ethan-1-one (4.4db): Following the general procedure (condition b), the reaction between 1-(4-methoxybenzylidene)-2-phenylhydrazine (0.5 mmol, 113 mg) with Methyl vinyl ketone (1.0 mmol, 70.0 mg, 83.23 µl) yielded the desired product 1-(3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)ethan-1-one as a white solid in 54% yield (78.8 mg).



Chemical Formula: $C_{18}H_{16}N_2O_2$

Melting point 98-100°C.

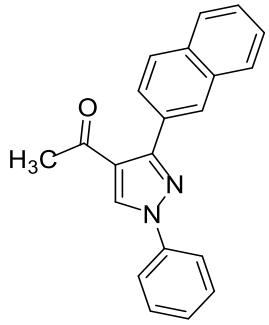
FT-IR (ATR): ν_{max}= 2926, 2844, 1670, 1605, 1514, 1446 1289 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.43 (s, 1H), 7.77- 7.71 (m, 4H), 7.49 –7.46 (m, 2H), 7.36- 7.33 (m, 1H), 6.97 (d, *J*= 8.8 Hz, 2H), 3.84 (s, 3H), 2.40 (s, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ = 192.6, 160.3, 153.4, 139.3, 131.7, 130.8 (2C), 129.7 (2C), 127.6, 124.9, 122.7, 119.7 (2C), 113.7 (2C), 55.4, 29.4 ppm

MS (ESI) calcd for $C_{18}H_{17}N_2O_2$ $[M+H]^+$ 293.1285 found 293.1312.

1-(3-(naphthalen-2-yl)-1-phenyl-1*H*-pyrazol-4-yl)ethan-1-one (4.4eb): Following the general procedure (condition b), the reaction between 1-(naphthalen-2-ylmethylene)-2-phenylhydrazine (0.5 mmol, 123 mg) with Methyl vinyl ketone (1.0 mmol, 70 mg, 83.23 µl) yielded the desired product 1-(3-(naphthalen-2-yl)-1-phenyl-1*H*-pyrazol-4-yl)ethan-1-one as a white solid in 55% yield (85.8 mg).



Chemical Formula: $C_{21}H_{16}N_2O$

Melting point 113-115°C.

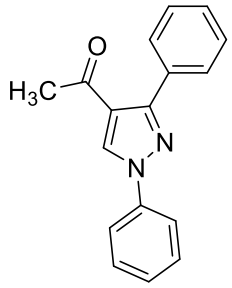
FT-IR (ATR): ν_{max}= 3055, 2923, 1716, 1518, 1432, 1227 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.48 (s, 1H), 8.31 (s, 1H), 7.93- 7.84 (m, 4H), 7.81- 7.79 (m, 2H), 7.52- 7.48 (m, 4H), 7.39- 7.35 (m,1H), 2.42 (s, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ = 192.6, 153.6, 139.3,133.6, 133.2, 131.9, 130.0, 129.8 (2C), 128.9, 128.6, 127.8, 127.7, 127.2, 126.6, 126.3, 123.2, 119.8 (2C), 29.5 ppm

MS (ESI) calcd for $C_{21}H_{17}N_2O$ $[M+H]^+$ 313.1335 found 313.1397.

1-(1,3-diphenyl-1*H*-pyrazol-4-yl)ethan-1-one (4.4ab): Following the general procedure (condition b), the reaction between 1-benzylidene-2-phenylhydrazine (0.5 mmol, 98 mg) with Methyl vinyl ketone (1.0 mmol, 70.0 mg, 83.23 µl) yielded the desired product 1-(1,3-diphenyl-1*H*-pyrazol-4-yl)ethan-1-one as an oily liquid in 65% yield (93.5 mg).



Chemical Formula: $C_{17}H_{14}N_2O$

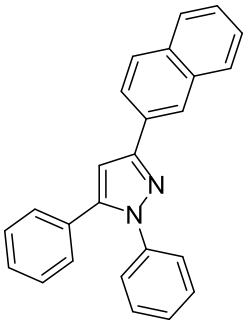
FT-IR (ATR): ν_{max}= 3061, 2923, 1670, 1597, 1514, 1445 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.4(s, 1H), 7.78- 7.73 (m, 4H), 7.50- 7.34 (m, 6H), 2.38 (s, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ = 192.6, 153.6, 139.3,133.6, 133.2, 131.9, 130.0, 129.8 (2C), 128.9, 128.6, 127.8, 127.7, 127.2, 126.6, 126.3, 123.2, 119.8 (2C), 29.5 ppm

MS (ESI) calcd for $C_{21}H_{17}N_2O$ $[M+H]^+$ 263.1179 found 263.1234.

3-(naphthalen-2-yl)-1,5-diphenyl-1*H*-pyrazole (4.3ea): Following the general procedure (condition a), the reaction between 1-(naphthalen-2-ylmethylene)-2-phenylhydrazine (0.5 mmol, 123 mg) with *trans*-β-nitrostyrene (0.6 mmol, 89.4 mg) yielded the desired product 3-(naphthalen-2-yl)-1,5-diphenyl-1*H*-pyrazole as a white solid in 71% yield (122 mg).



Chemical Formula: $C_{25}H_{18}N_2$

Melting point 174-176°C.

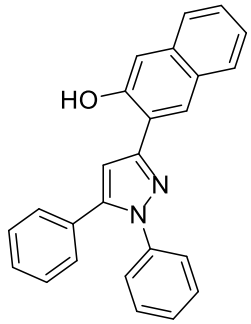
FT-IR (ATR): ν_{max}= 3052, 1596, 1548, 1496, 1317, 1261 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.39(s, 1H), 8.12- 8.09 (s, 1H), 7.93- 7.84 (m, 3H), 7.52- 7.30 (m,12H), 6.97 (s, 1H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ = 152.2, 144.7, 140.3, 133.7, 133.4, 130.7, 130.6, 129.1 (2C), 128.9 (2C), 128.6 (2C), 128.5, 128.4, 128.38, 127.9, 127.6, 126.3, 126.0, 125.5 (2C), 124.5, 124.3, 105.6 ppm

MS (ESI) calcd for $C_{25}H_{19}N_2$ $[M+H]^+$ 347.1543 found 347.1790.

3-(1,5-diphenyl-1*H*-pyrazol-3-yl)naphthalen-2-ol (4.3fa): Following the general procedure (condition a), the reaction between 3-((2-phenylhydrazono)methyl)naphthalen-2-ol (0.5 mmol, 131 mg) with *trans*-β-nitrostyrene (0.6 mmol, 89.4 mg) yielded the desired product 3-(1,5-diphenyl-1*H*-pyrazol-3-yl)naphthalen-2-ol as a white solid in 63% yield (114 mg).



Chemical Formula: $C_{25}H_{18}N_2O$

Melting point 192-194°C.

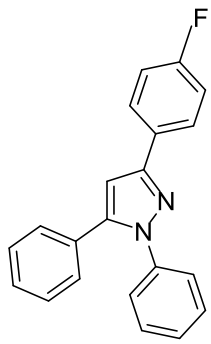
FT-IR (ATR): ν_{max}**=** 3053, 2922, 1597, 1496, 1407, 1341, 1230 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$) δ = 8.44 (d, J= 8.4 Hz, 1H), 7.85-7.77 (m, 2H), 7.53- 7.48 (m, 1H), 7.41- 7.31 (m, 12H), 7.25 (s, 1H), 7.08 (s, 1H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ = 154.1, 149.6, 144.3, 139.5, 132.1, 130.5, 130.1, 129.2 (2C), 129.1, 129.0 (2C), 128.9, 128.84, 128.80 (2C), 127.9, 126.9, 125.2 (2C), 124.0, 123.1, 119.1, 109.8, 109.6 ppm

MS (ESI) calcd for $C_{25}H_{19}N_2O$ $[M+H]^+$ 363.1492 found 363.1720.

3-(4-fluorophenyl)-1,5-diphenyl-1*H*-pyrazole (4.3ba): Following the general procedure (condition a), the reaction between 1-(4-fluorobenzylidene)-2-phenylhydrazine (0.5 mmol, 115 mg) with *trans*-β-nitrostyrene (0.6 mmol, 89.4 mg) yielded the desired product 3-(4-fluorophenyl)-1,5-diphenyl-1*H*-pyrazole as a white solid in 69% yield (113.8 mg).



Chemical Formula: $C_{22}H_{18}FN_2$

Melting point 99-101°C.

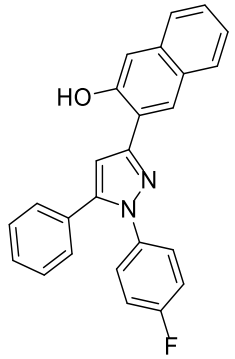
FT-IR (ATR): ν_{max}**=** 2925, 1725, 1599, 1493, 1444, 1354, 1277cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.91- 7.86 (m, 2H), 7.37-7.25 (m, 10H), 7.14- 7.09 (m, 2H), 6.77 (s, 1H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ = 162.8 ($1J_{CF}$= 245.4 Hz), 151.2, 144.6, 140.1, 130.5, 129.4 ($4J_{CF}$= 3.3 Hz), 129.0, 128.7 ($2J_{CF}$= 22.1 Hz, 3C), 128.5 (2C), 127.6 ($3J_{CF}$= 7.9 Hz), 125.4 (3C), 115.8 (2C), 115.5 (2C), 105.1 ppm

HRMS (ESI) calcd for $C_{21}H_{16}FN_2$ $[M+H]^+$ 315. 1292 found 315.1295.

3-(1-(4-fluorophenyl)-5-phenyl-1*H*-pyrazol-3-yl)naphthalen-2-ol (4.3ga): Following the general procedure (condition a), the reaction between 3-((2-(4-fluorophenyl)hydrazono)methyl)naphthalen-2-ol (0.5 mmol, 140 mg) with *trans*-β-nitrostyrene (0.6 mmol, 89.4 mg) yielded the desired product 3-(1-(4-fluorophenyl)-5-phenyl-1*H*-pyrazol-3-yl)naphthalen-2-ol as a white solid in 45% yield (85.5 mg).



Chemical Formula: $C_{25}H_{17}FN_2O$

Melting point 133-135°C.

FT-IR (ATR): ν_{max}**=** 3058, 2922, 1603, 1511, 1342, 1227 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.40 (d, *J*= 8.0 Hz, 1 H), 7.83- 7.76 (m, 2H), 7.51- 7.47 (m, 1H), 7.39-7.29 (m, 10H), 7.10- 7.06 (m, 3H) ppm

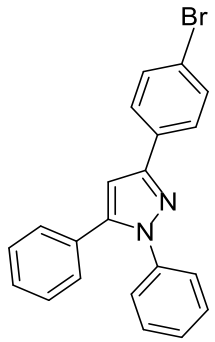
^{13}C NMR (100 MHz, $CDCl_3$) δ = 161.9 ($^1J_{CF}$= 246.8 Hz), 153.9, 149.7, 144.4, 135.6, 132.0, 130.5, 129.8, 129.0, 128.9 (2C), 128.88 (2C), 123.95, 123.2, 119.0, 116.3, 116.0, 109.7, 109.6 ppm

MS (ESI) calcd for $C_{25}H_{18}FN_2O$ $[M+H]^+$ 381.1398 found 381.1452.

3-(4-bromophenyl)-1,5-diphenyl-1*H*-pyrazole (4.3ca): Following the general procedure (condition a), the reaction between 1-(4-bromobenzylidene)-2-phenylhydrazine (0.5 mmol, 145 mg) with *trans*-β-nitrostyrene (0.6 mmol, 89.4 mg) yielded the desired product 3-(4-bromophenyl)-1,5-diphenyl-1*H*-pyrazole as a white solid in 56% yield (109 mg).

Chemical Formula: $C_{22}H_{18}BrN_2$

Melting point 159-161 °C.

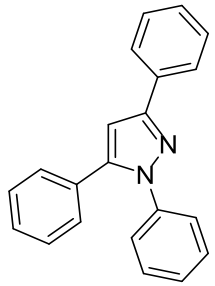


FT-IR (ATR): ν_{max}= 2960, 2924, 1727, 1594,1259, 1020 cm^{-1}; **^{1}H NMR (400 MHz, $CDCl_3$) δ** = 7.810- 7.78 (m, 2H), 7.56-7.53 (m, 2H), 7.36- 7.26 (m, 10 H), 6.79 (s, 1H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ = 151.0, 144.7, 140.1, 132.1, 131.9 (2C), 130.4, 129.1 (2C), 128.8 (2C), 128.6 (2C), 128.5, 127.7, 127.4 (2C), 125.4 (2C), 122.0, 105.2 ppm

MS (ESI) calcd for $C_{21}H_{16}BrN_2$ $[M+H]^+$ 375.0491 found 375.0529.

1,3,5-triphenyl-1*H*-pyrazole (4.3aa): Following the general procedure (condition a), the reaction between 1-benzylidene-2-phenylhydrazine (0.5 mmol, 196 mg) with *trans*-β-nitrostyrene (0.6 mmol, 89.4 mg) yielded the desired product 1,3,5-triphenyl-1*H*-pyrazole as a white solid in 75% yield (111 mg).



Chemical Formula: $C_{21}H_{16}N_2$

Melting point 137-139 °C.

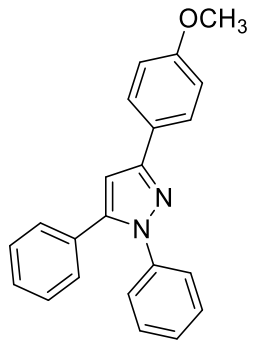
FT-IR (ATR): ν_{max}= 2920, 2856, 1732, 1543, 1363, 1260, 1211 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.94- 7.91(m, 1H), 7.45-7.41 (m, 2H), 7.39- 7.27 (m, 1H), 6.83 (s,1H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ = 152.1, 144.5, 140.3, 133.2, 130.7, 129.0 (2C), 128.9 (2C), 128.8 (2C), 128.6 (2C), 128.4, 128.1, 127.5, 125.9 (2C), 125.4 (2C), 105.3 ppm

MS (ESI) calcd for $C_{21}H_{17}N_2$ $[M+H]^+$ 297.1386 found 297.1395.

3-(4-methoxyphenyl)-1,5-diphenyl-1*H*-pyrazole (4.3da): Following the general procedure (condition a), the reaction between 1-benzylidene-2-phenylhydrazine (0.5 mmol, 196 mg) with *trans*-β-nitrostyrene (0.6 mmol, 89.4 mg) yielded the desired product 1,3,5-triphenyl-1*H*-pyrazole as a white solid in 75% yield (111 mg).



Chemical Formula: $C_{22}H_{18}N_2O$

Melting point 135-137 °C.

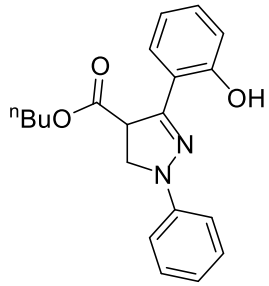
FT-IR (ATR): ν_{max}**=** 3050, 2926, 2840, 1597, 1484, 1345, 1237, 1168, 1021 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.85 (d, *J* = 8.0 Hz, 2H), 7.37-7.27 (m, 10H), 6.96 (d, *J* = 8 Hz, 2H), 6.75 (s, 1H), 3.85 (s, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.6, 151.8, 144.3, 140.2, 130.7, 128.9, 128.8, 128.4, 128.2, 127.3, 127.1, 125.9, 125.3, 114.1, 104.8, 55.3. ppm

MS (ESI) calcd for $C_{22}H_{19}N_2O$ $[M+H]^+$ 327.1492 found 327.1759

butyl 3-(2-hydroxyphenyl)-1-phenyl-4,5-dihydro-1*H*-pyrazole-4-carboxylate (4.7ic): Following the general procedure (condition c), the reaction between 2-((2-phenylhydrazono)methyl)phenol (0.5 mmol, 106 mg) with n-butyl acrylate (0.6 mmol, 76.8 mg, 85.9 µl) yielded the desired product butyl 1,3-diphenyl-4,5-dihydro-1*H*-pyrazole-4-carboxylate as a white solid in 30% Yield (51 mg).



Chemical Formula: $C_{20}H_{22}N_2O_3$

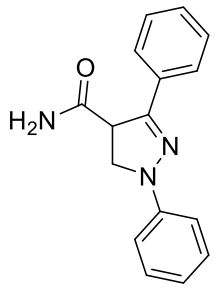
FT-IR (ATR): ν_{max}**=** 3199, 1731, 1587, 1489, 1223, 1145 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.52 (s, 1H), 7.37- 7.30 (m, 3H), 7.18- 7.16 (m, 1H), 7.06- 7.01 (m, 3H), 6.94- 6.89 (m, 2H), 4.82- 4.77 (q, J= 6.8 Hz, 1H), 4.21- 4.11 (m, 2H), 3.76 (dd, J= 12.4 Hz, 1H), 3.53 (dd, J= 6.8 Hz, 1H), 1.62- 1.51 (m, 2H), 1.29- 1.22 (m, 2H), 0.85 (t, J= 7.6 Hz, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.2, 157.2, 149.7, 143.9, 130.9, 129.4 (2C), 127.2, 120.6, 119.5, 116.8, 115.9, 113.2 (2C), 65.9, 60.8, 38.7, 30.5, 19.0, 13.7 ppm

MS (ESI) calcd for $C_{20}H_{23}N_2O_3$ $[M+H]^+$ 339.1703 found 339.1731.

1,3-diphenyl-4,5-dihydro-1*H*-pyrazole-4-carboxamide (4.8ad): 1-benzylidene-2-phenylhydrazine (0.5 mmol, 196 mg) was added to an oven-dried Schlenk tube equipped with a magnetic stirrer. To this, acrylonitrile (1 mmol, 53.1 mg) and $AlCl_3$ (0.5 mmol) were added, and the reaction mixture was stirred at 70°C in 2 ml TFA. The product formed was isolated from column chromatography. The product 1,3-diphenyl-4,5-dihydro-1*H*-pyrazole-4-carboxamide obtained was a white solid, in 53% yield (70 mg).



Chemical Formula: $C_{16}H_{15}N_3O$

FT-IR (ATR): ν_{max}= 3370, 3188, 2920, 2854, 1730, 1654, 1599, 1503, 1185 cm^{-1}

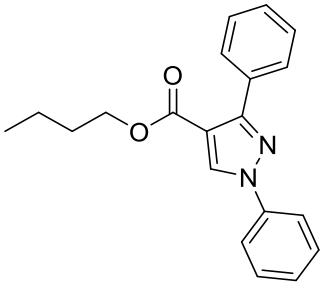
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.93 (s, 1H), 7.74- 7.72 (m, 2H), 7.4- 7.23 (m, 6H), 7.07 (d, J= 7.6 Hz, 2H), 6.79 (t, J= 7.2 Hz, 1H,), 4.44 (dd, 1H, J= 7.2 Hz), 4.11 (t, 1H, J= 10.4), 3.96 (dd, 1H, J= 7.2 Hz) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.8, 147.8, 145.2, 132.6, 129.6 (2C), 129.1 (2C), 128.9, 126.2 (2C), 119.3, 113.1 (2C), 53.8, 51.0 ppm

MS (ESI) calcd for $C_{16}H_{16}N_3O$ $[M+H]^+$ 266.1288 found 266.1567

4.4.4 Single Crystal X-ray Data of the Compound 4.6ac

Compound 4.6ac



CCDC No: 2130385

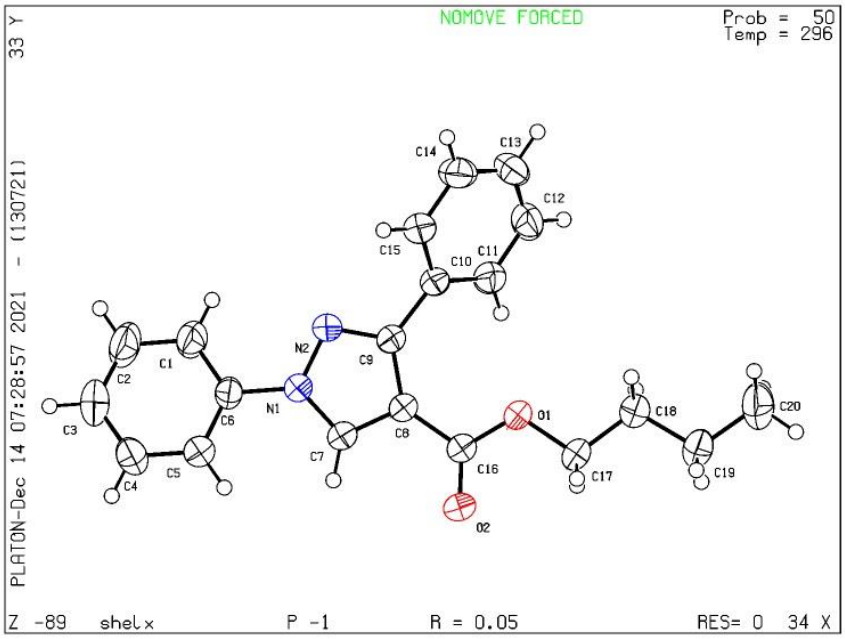


Figure 4.19 ORTEP diagram of the Compound **4.6ac**

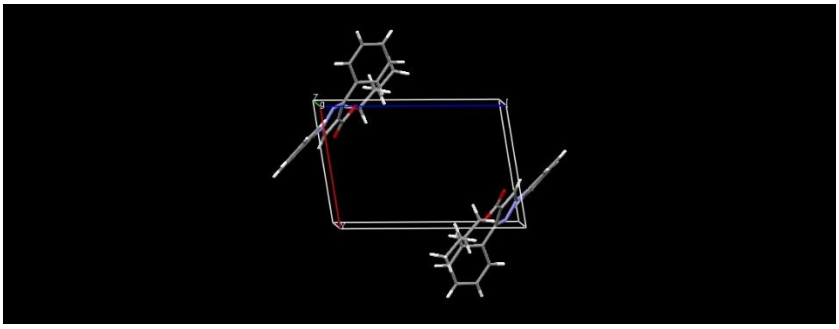


Figure 4.20 Crystal packing of the Compound **4.6ac**

Crystal data and structure refinement for Compound *RBP-4-56A* – CCDC No:

Identification code	shelx
Empirical formula	C_{20} H_{20} N_2 O_2
Formula weight	320.38
Temperature	296(2) K
Wavelength	0.71073 A
Crystal system, space group	Triclinic, P -1
Unit cell dimensions	a = 7.9240(12) A alpha = 69.202(8) deg.
	b = 10.0608(17) A beta = 74.217(7) deg.
	c = 12.170(2) A gamma = 72.220(7) deg.

Volume	848.9(2) A^3
Z, Calculated density	2, 1.253 Mg/m^3
Absorption coefficient	0.082 mm^-1
F(000)	340
Crystal size	0.500 x 0.400 x 0.350 mm
Theta range for data collection	2.746 to 28.313 deg.
Limiting indices	-10<=h<=6, -13<=k<=13, -15<=l<=15
Reflections collected / unique	9938 / 3986 [R(int) = 0.0281]
Completeness to theta = 25.242	99.2 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.972 and 0.960
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3986 / 0 / 219
Goodness-of-fit on F^2	1.040
Final R indices [I>2sigma(I)]	R1 = 0.0482, wR2 = 0.1213
R indices (all data)	R1 = 0.0823, wR2 = 0.1438
Extinction coefficient	0.033(5)
Largest diff. peak and hole	0.214 and -0.154 e.A^-3

Appendix III

Representative spectra of some of the final compounds are shown:

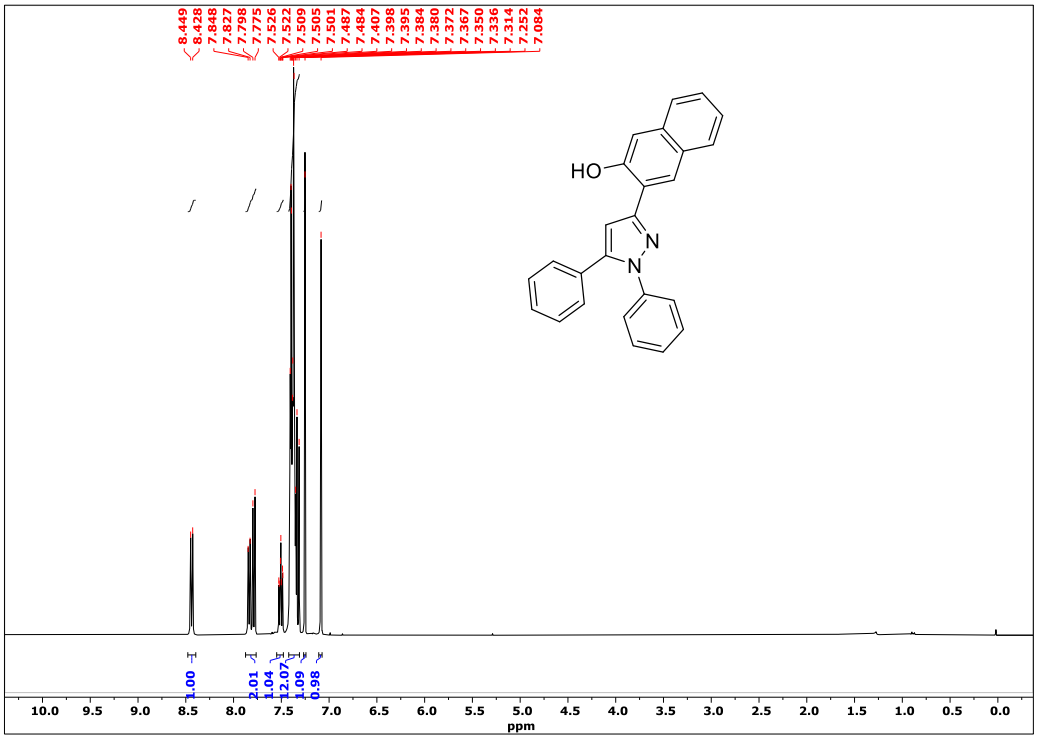


Figure 4.21 ^{1}H NMR spectrum of **4.3fa**

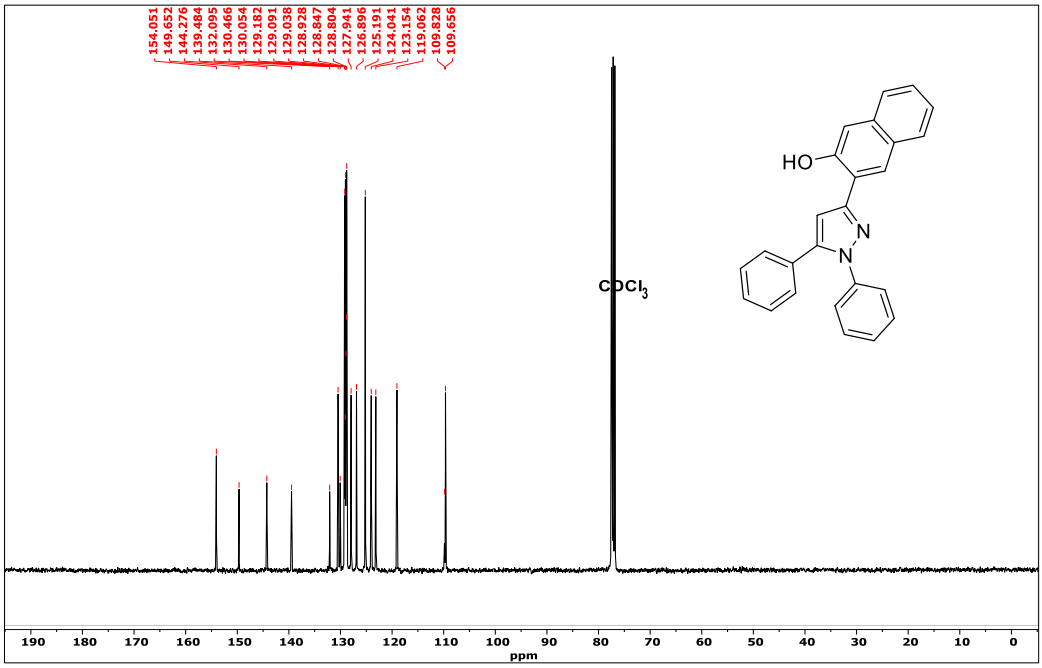


Figure 4.22 ^{13}C NMR spectrum of **4.3fa**

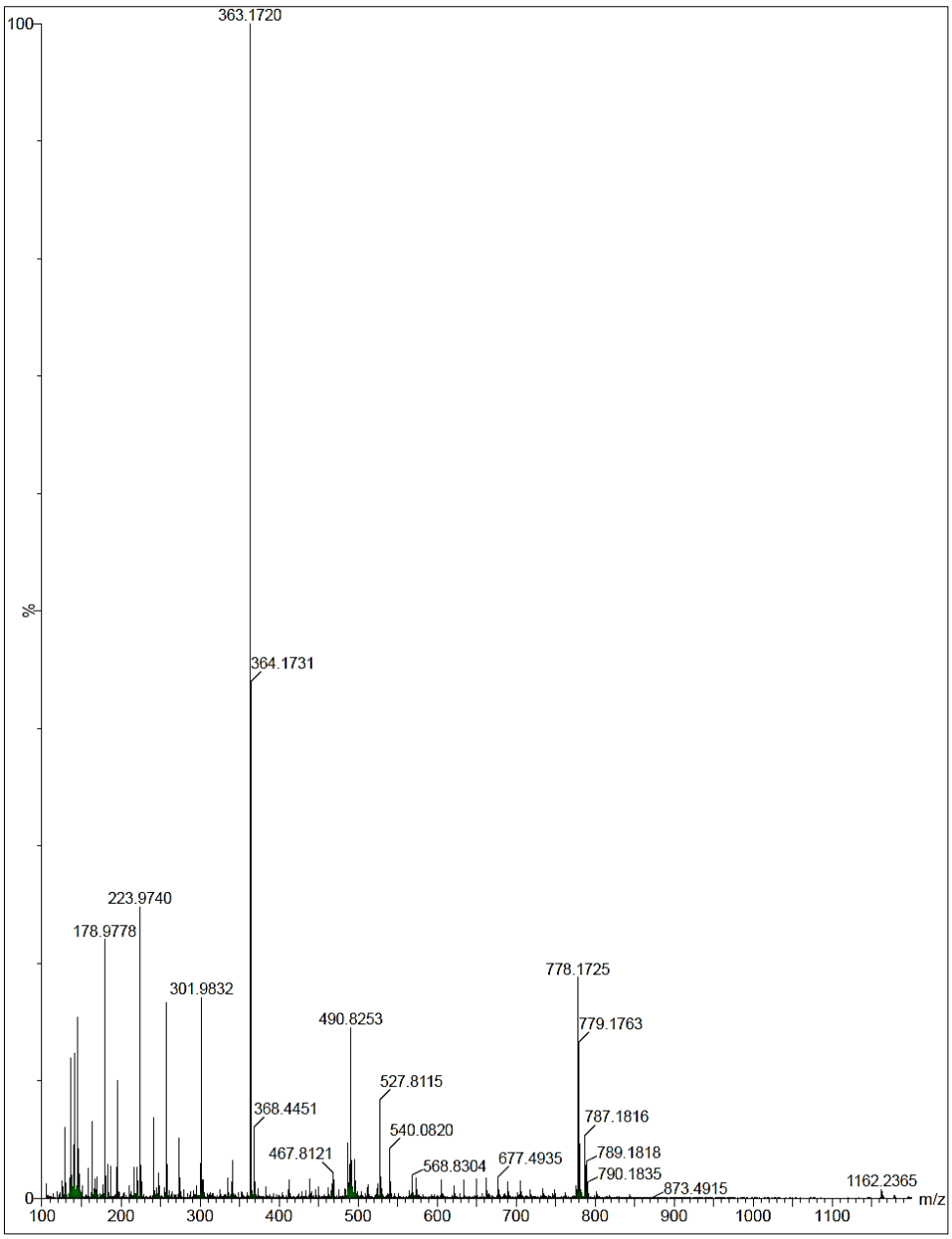


Figure 4.23 Mass spectrum of **4.3fa**

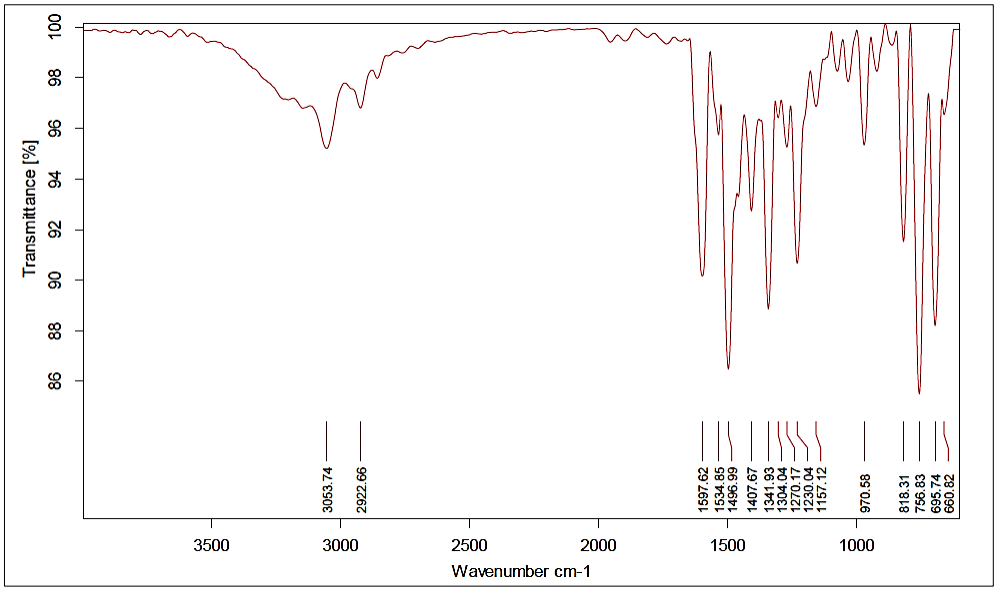


Figure 4.24 FT-IR spectrum of **4.3fa**

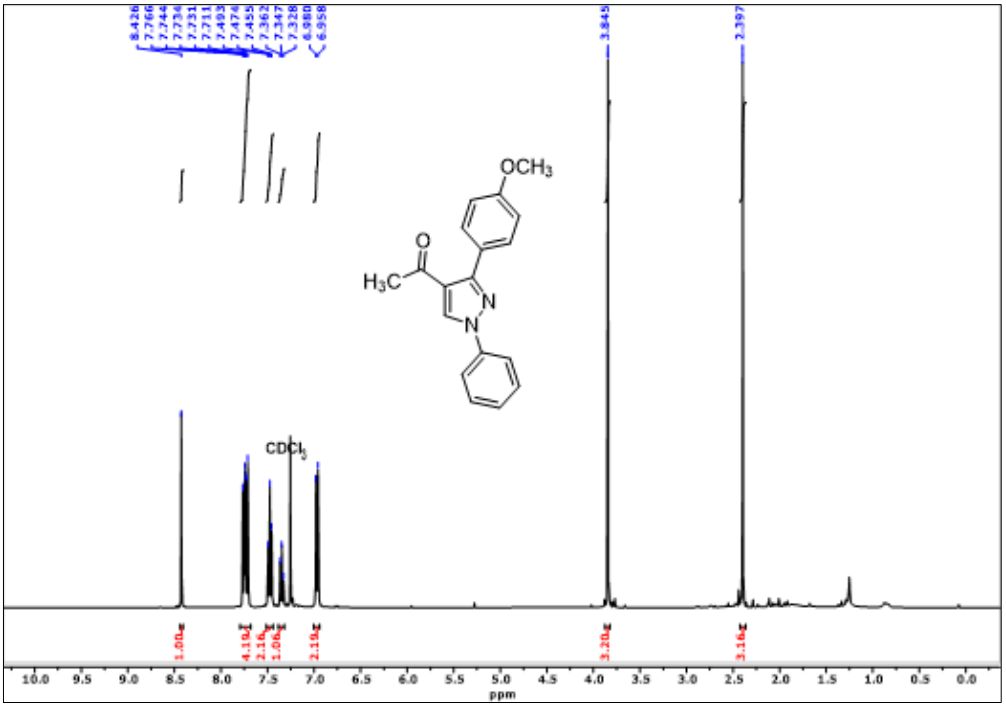


Figure4.25 ^{1}H NMR spectrum of **4.4db**

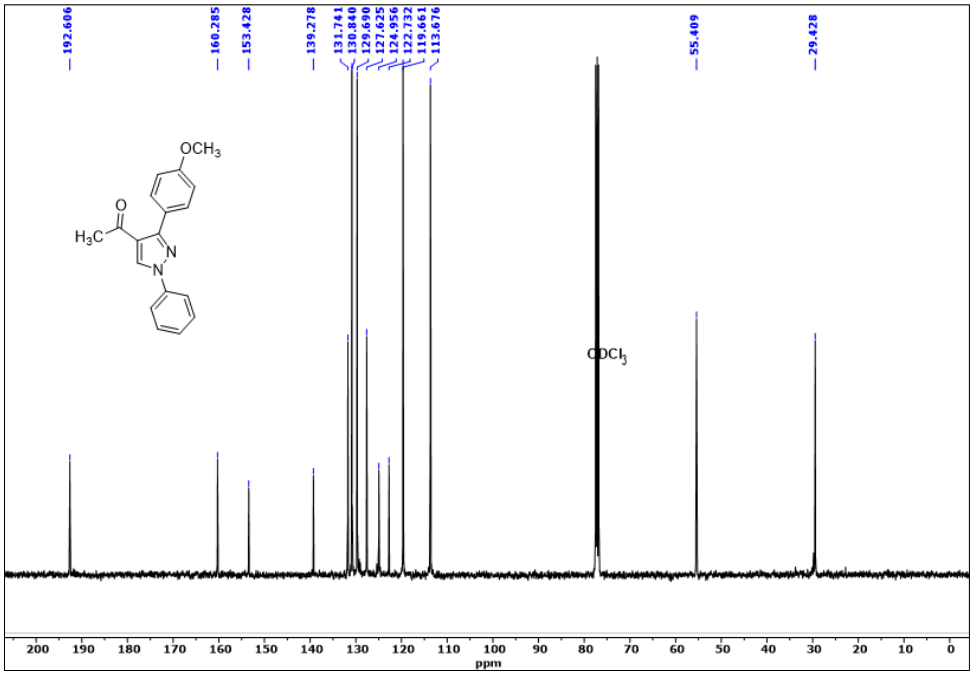


Figure 4.26 ^{13}C NMR spectrum of **4.4db**

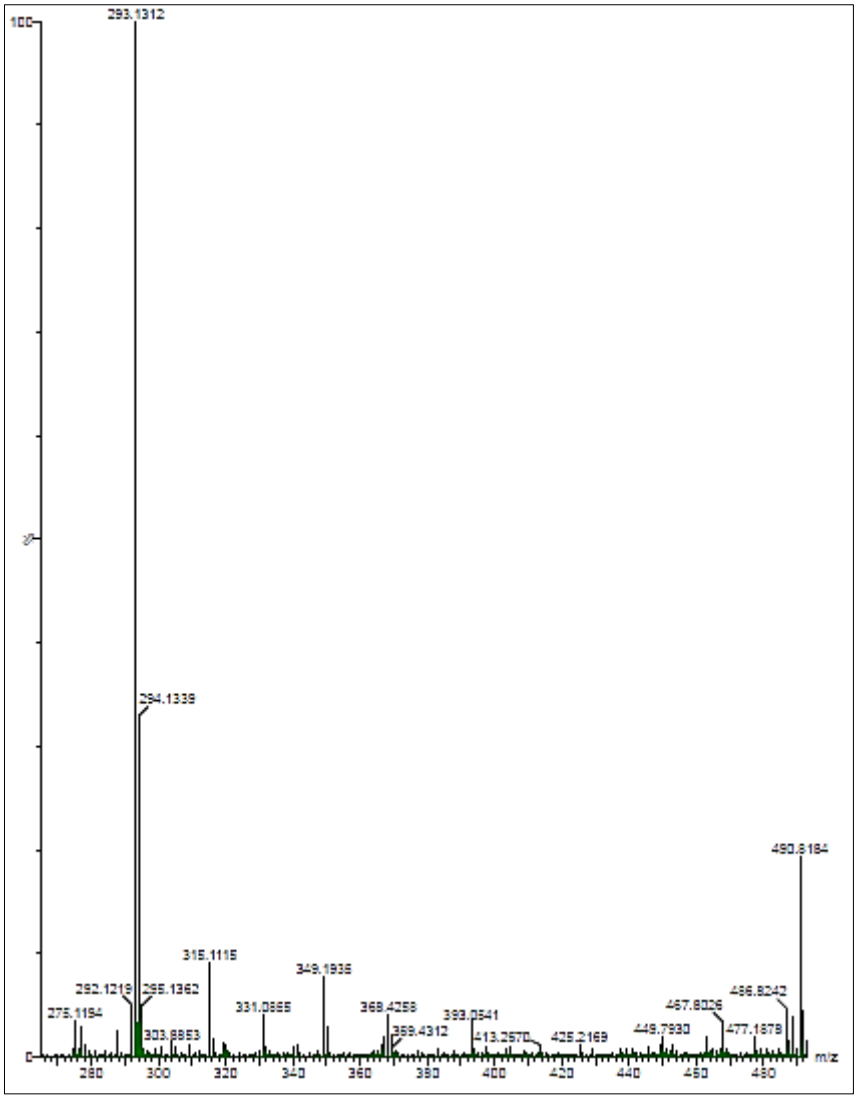


Figure 4.27 Mass spectrum of **4.4db**

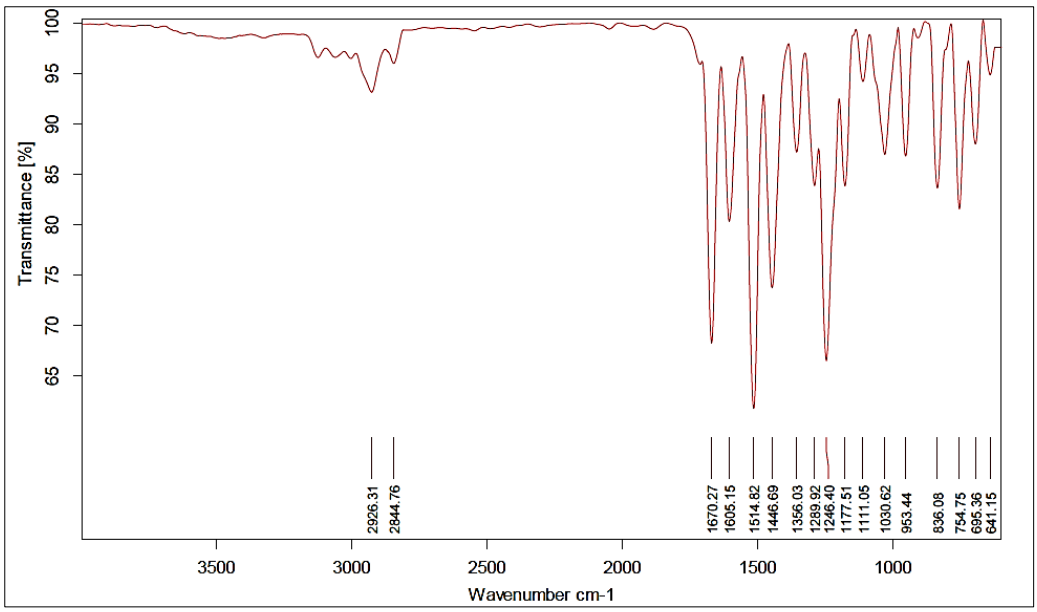


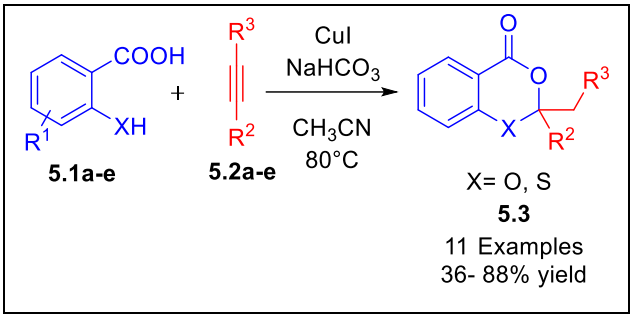
Figure 4.28 FT-IR spectrum of **4.4db**

CHAPTER 5

SYNTHESIS OF FUNCTIONALIZED BENZO [1,3] DIOXIN-4-ONES FROM SALICYLIC ACID AND ACETYLENIC ESTERS AND THEIR DIRECT AMIDATION

Abstract

Direct synthesis of 4H-benzo[d][1,3]dioxin-4-one derivatives from salicylic acids and acetylenic esters has been described. Both mono- and di- substituted acetylenic esters react with salicylic acids to form benzodioxinones. An efficient strategy for the synthetic transformation of benzodioxinones to salicylamide derivatives at room temperature is also described.



5.1 INTRODUCTION

Heterocycles and their derivatives play a pivotal role in natural products and synthetic organic chemistry. Isolation, bio and chemical synthesis, and investigation of pharmacological and biological properties of diverse heterocycles have attracted both organic and medicinal chemists (Arora et al. 2012; Panda et al. 2016). It is a highly vibrant and ever-expanding field of research. Besides, heterocycle scaffolds contribute significantly towards the development of novel organic materials for the luminescent applications due to their unique photophysical properties, which can be tuned to suit diverse applications (Ke et al. 2020; Mishra and Bäuerle 2012; Pron et al. 2010). Fused heterocyclic cores are a potentially active component in many pharmacological medications and agrochemicals on the market. It's commonly utilized for the manufacture of OLEDs, dyes, biosensors, light trapping devices, receptor molecules, and other things besides medicine. Chemical entities with various biological, physical, and chemical properties are constructed by developing and synthesizing novel benzo fused heterocycles. Crolibulin (anticancer agent), chloroquine (antimalarial medicine), doxycycline (antibiotic), rubicordiofolin (cytotoxic activity), and vilazodone (antidepressant drug) are some of the notable benzo-fused core based drugs. Fluorescein (natural colour), tryptophan (essential amino acid), saccharin

(manufactured sweetener), and galaxolide (synthetic musk) are all examples of benzo fused heterocycles which finds extensive applications in industrial research. Benzodioxans are oxygen-based isomeric heterocycles with various applications in medicinal, agricultural, and synthetic chemistry. Among the isomeric benzodioxans, 1,3-benzodioxane and 1,4-benzodioxane are used in medicinal and agrochemicals research. In addition, they are potential synthetic intermediates in multistep organic synthesis (Elliott et al. 2016; Evans et al. 2012; Yoshino et al. 2012).

5.2 BENZODIOXINONE DERIVATIVES AND THEIR APPLICATIONS

Benzodioxinones and their derivatives are the particular class of heterocycles in which the dioxinone moiety is attached to benzene or substituted benzene part. Benzodioxinone is not a common heterocyclic moiety present in the natural product. However, it received attention because it is a precursor for synthesizing various drug molecules and synthetic building blocks in numerous organic processes. They exhibit potential biological activities, including antifungal, antimicrobial, cytotoxic, and antiplasmodial, and are also used as the precursor for synthesizing various potentially important drug molecules. Several unique methods have been developed for the synthesis of this Benzodioxinone core over many years. Michael cascade approach, tandem hydroxylation, etherification, oxidative cyclization promoted by AgOAc, etc., are some of the approaches for synthesizing this heterocyclic structure. Benzodioxinones are one of the major cores present in various natural products and hence is the key intermediate in various total synthesis routes.

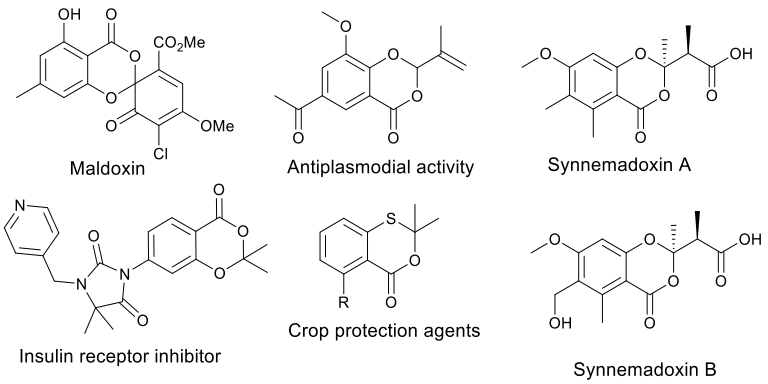


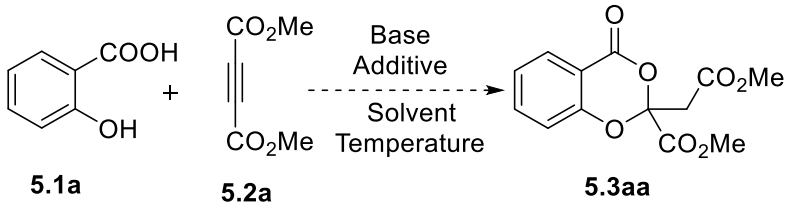
Figure 5.1 Drug/Agrochemicals containing benzodioxinone/benzothiine core

5.3 PRESENT WORK

From the literature (summarized in chapter 1, part C), we understand that the reaction between salicylic acid and acetylenic esters is not yet explored in detail though the analogous thiosalicylic acid-based methods have been well documented. We started our investigations using the salicylic acid **5.1a** and dimethyl acetylenedicarboxylate (DMAD) **5.2a** as the model substrates. Stirring **5.1a** (0.6 mmol) and **5.2a** (0.5 mmol) together in a Schlenk tube using acetonitrile (2 ml) as the solvent resulted in no characteristic reaction at room temperature as well as at 80°C.

5.3.1 Effect of the base on the reaction

We further introduced a base into the reaction medium. And the observations are summarized in **Table 5.1**. Both organic and inorganic bases were screened to identify the best condition. Organic bases such as pyridine and DABCO failed to afford the expected product under hot conditions. Interestingly, inorganic bases succeeded in yielding the expected benzo[d] [1,3]dioxin-4-one with moderate conversion. When the reaction was carried out using salicylic acid (0.6 mmol, 82.8 mg) and DMAD (0.5 mmol, 71.0 mg) in presence of $NaHCO_3$ (0.6 mmol, 50.4 mg) in acetonitrile at 80°C, we could isolate 55% of Methyl-2-(2-methoxy-2-oxoethyl)-4-oxo-4H-benzo[d][1,3]dioxine-2-carboxylate (**5.3aa**) as the final product.



Scheme 5.1

Sl. No.	Base (equiv.)	Additives	Solvent	Temperature (°C)	Yield (%)
1	Pyridine (10 mol%)	----------	CH_3CN	80	nr
2	DABCO (10 mol%)	----------	CH_3CN	80	nr
3	K_2CO_3 (20 mol%)	----------	CH_3CN	80	Trace
4	$NaHCO_3$ (20 mol%)	----------	CH_3CN	80	40

5	$NaHCO_3$ (1.2 equiv.)	----------	CH_3CN	80	55
Conditions: Salicylic acid (1.2 equiv.), DMAD (1 equiv.), acetonitrile (2 ml) in Schlenk tube at 80°C.					

Table 5.1 Studies on the effect of bases

The product **5.3aa** obtained after the reaction was isolated by column chromatography and the structure was characterized by standard FT-IR, NMR and HRMS analysis, and was in agreement with the expected benzodioxinones derivative. In the IR spectrum of the compound, the absorption band at 1757 cm^{-1} corresponds to the ester C=O stretching frequency. The six $–OCH_3$ protons appears as a sharp singlet at δ= 3.68 ppm in the ^1H NMR spectrum. Two protons on the aliphatic carbon atom exhibit a peak at δ= 3.37-3.25 (m, 2H) ppm (**Figure 5.2**). The peaks at δ= 165.9 ppm and δ= 165.1 ppm in the ^{13}C NMR spectrum depicts the carbonyl carbon atoms of the ester group and lactone ring, respectively. Methoxy carbon atoms resonate at δ=51.4 ppm and δ= 52.7 ppm, whereas the quaternary carbon on the six-membered ring exhibits a unique peak at δ= 99.6 ppm (**Figure 5.3**). Finally, the mass of the compound was also confirmed from the HR-MS analysis (**Figure 5.4**).

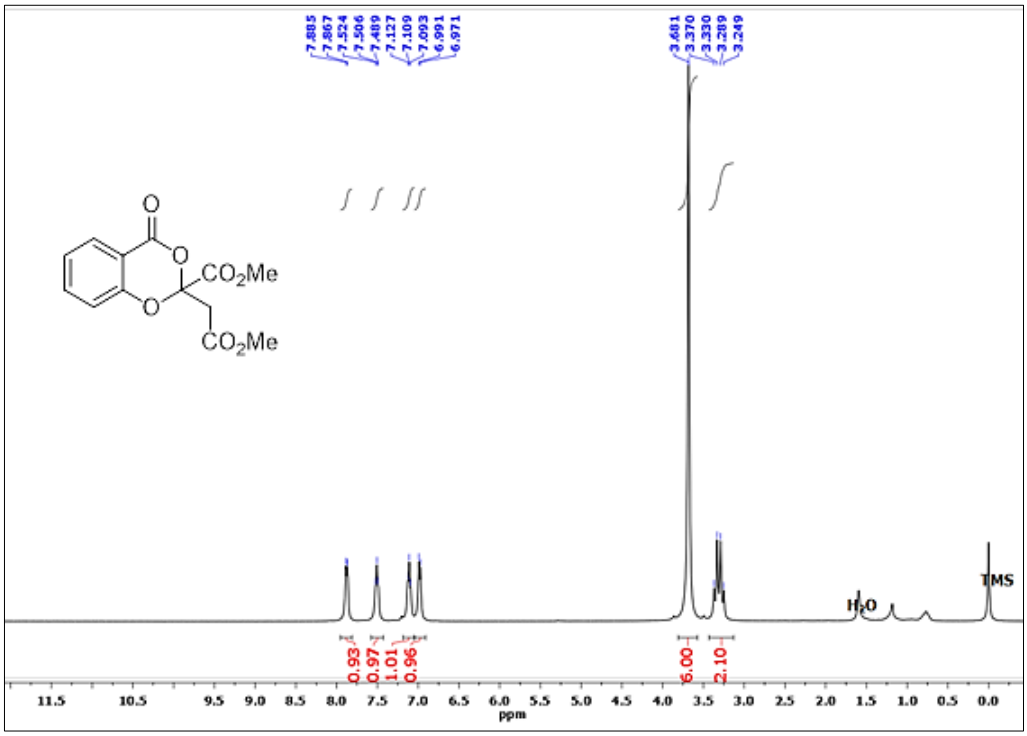


Figure 5.2 ^1H NMR spectrum of **5.3aa**

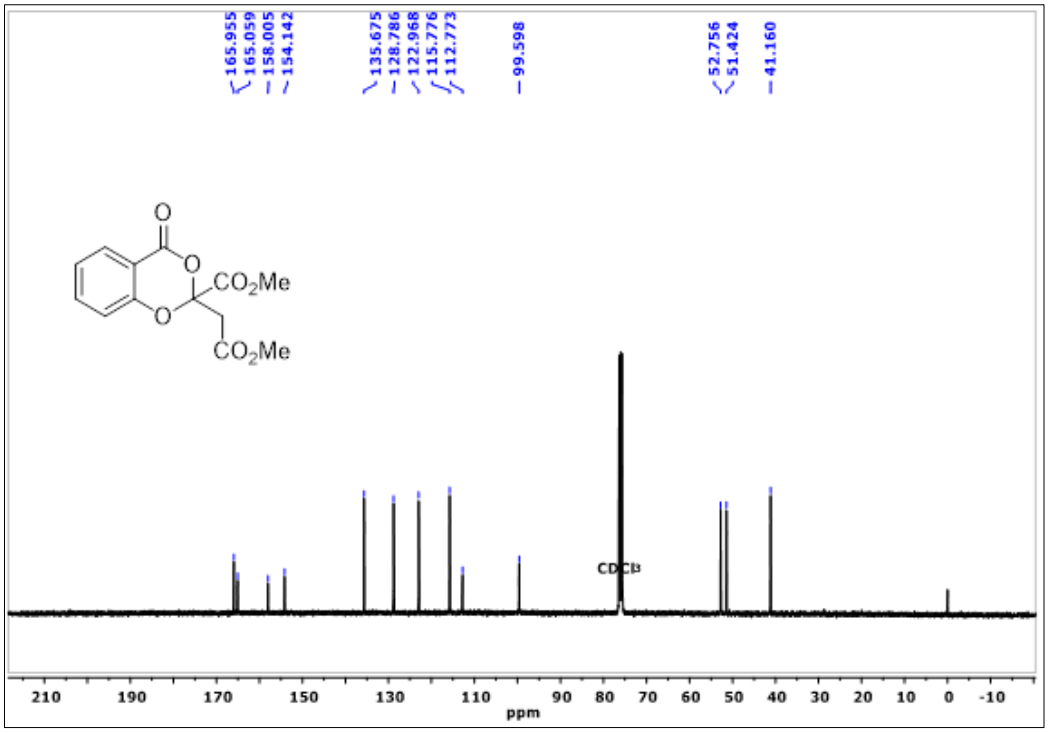


Figure 5.3 ^{13}C NMR spectrum of **5.3aa**

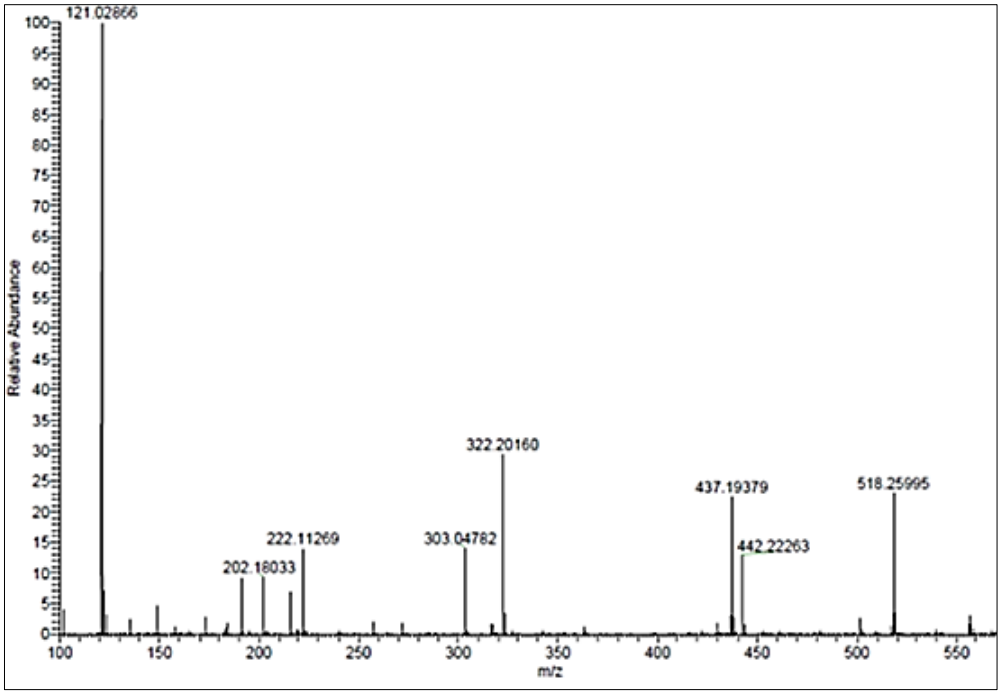


Figure 5.4 HRMS spectrum of **5.3aa**

After confirming the structure, further optimization studies were carried out to obtain the maximum yield.

5.3.2 Screening of the additives for the reaction.

To improve the electrophilicity of the acetylenic bond, we introduced some metal salts along with the base to the reaction medium, expecting the co-ordination of M^+ ions with the alkyne bond. We studied the effect of different metal salts such as CuI, $Pd(OAc)_2$, CuCl, $FeCl_3$, $NiCl_2$, and $MnCl_2$ in the reaction. Among the various metal salts screened, CuI showed a remarkable influence on the reaction outcome as summarized in **Table 5.2**.

Sl. No.	Base (equiv.)	Additives	Solvent	T (°C)	Yield (%)
1	$NaHCO_3$ (1.2 equiv.)	CuI (20 mol%)	CH_3CN	80	<60
2	$NaHCO_3$ (1.2 equiv.)	CuI (1 equiv.)	CH_3CN	80	88
3	----------	CuI (1 equiv.)	CH_3CN	80	30
4	$NaHCO_3$ (1.2 equiv.)	$Pd(OAc)_2$ (10 mol%)	CH_3CN	80	45
5	$NaHCO_3$ (1.2 equiv.)	$FeCl_3$ (1 equiv)	CH_3CN	80	nr
6	$NaHCO_3$ (1.2 equiv.)	CuCl (1 equiv.)	CH_3CN	80	Trace
7	$NaHCO_3$ (1.2 equiv.)	$NiCl_2$ (1 equiv.)	CH_3CN	80	nr
8	$NaHCO_3$ (1.2 equiv.)	$MnCl_2$ (1 equiv.)	CH_3CN	80	nr
Conditions: Salicylic acid (1.2 equiv.), DMAD (1 equiv.), $NaHCO_3$ (1.2 equiv.) acetonitrile (2 ml) in Schlenk tube at 80°C.					

Table 5.2 Screening of the additives

$Pd(OAc)_2$ and CuCl yielded the product in trace amount, whereas other metal salts failed to yield the product. Stoichiometric CuI (1 equiv.) as an additive in the presence of $NaHCO_3$ (1.2 equiv.) enhanced the yield of the final benzo[d][1,3]dioxin-4-one derivative to 88% in 24 h. We noticed that both $NaHCO_3$ and CuI were crucial for the reaction as withdrawal of any of these reagents affected the overall conversion.

5.3.3. Effect of solvent on the reaction

After finalizing the base and additives, we moved further to optimize the solvent. Both polar protic and polar aprotic solvents were used to study the effect of solvent and

temperature on the reaction. THF and 1,2- DCE afforded the product in trace amount. The reaction was not at all proceeding in alcoholic solvent such as methanol. We ended up with a sluggish reaction mixture when the reaction was heated at 100°C in DMSO. Acetonitrile was finalized as the best solvent for the reaction after screening various solvents.

Sl. No.	**Base (equiv.)**	**Additives**	**Solvent**	**T (°C)**	**Yield (%)**
1	$NaHCO_3$ (1.2 equiv.)	CuI (1 equiv.)	CH_3CN	80	88
2	$NaHCO_3$ (1.2 equiv.)	CuI (1 equiv.)	1,2- DCE	80	Trace
3	$NaHCO_3$ (1.2 equiv.)	CuI (1 equiv.)	CH_3OH	60	nr
4	$NaHCO_3$ (1.2 equiv.)	CuI (1 equiv.)	THF	60	Trace
5	$NaHCO_3$ (1.2 equiv.)	CuI (1 equiv.)	DMSO	100	Sluggish reaction mixture
Conditions: Salicylic acid (1.2 equiv.), DMAD (1 equiv.), $NaHCO_3$ (1.2 equiv.), CuI (1 equiv.), solvent (2 ml) in schlenk tube.					

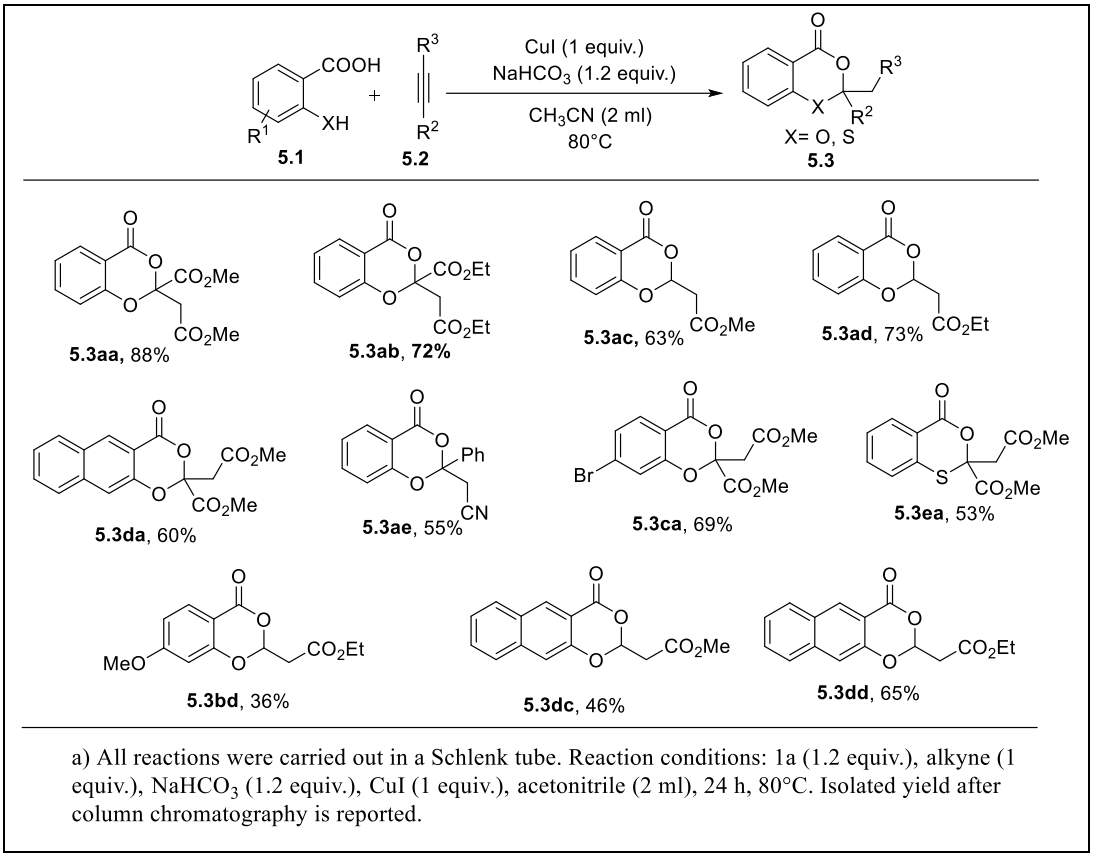
Table 5.3 Effect of solvents on the reaction

In short, after a series of optimization experiments, we identified the best reaction condition for the synthesis of **5.3aa**, treating **5.1a** and **5.2a** in acetonitrile in the presence of CuI (1 equiv.) and $NaHCO_3$ (1.2 equiv.) at 80°C for 24 h yielded 88% of the product.

5.4 SUBSTRATE SCOPE OF THE REACTION

With the optimized reaction conditions in hand, we subsequently explored the substrate scope of the reaction using various 2-hydroxy aromatic acids and acetylenic esters. Interestingly, both disubstituted acetylenic esters – such as DMAD **5.2a** and diethyl acetylenedicarboxylate **5.2b** – and monosubstituted propiolate esters – such as methyl propiolate **5.2c** and ethyl propiolate **5.2d** – were equally effective in the optimized conditions affording the benzo[d][1,3]dioxin-4-one derivatives in moderate to good

yields. Surprisingly, the hindered 3-phenylpropiolonitrile **5.2e** in place of acetylenic esters also afforded the expected product in 55% yield. Apart from salicylic acid, substituted salicylic acids – 4-methoxy derivative **5.1b** and 4-bromo derivative **5.1c** – were also used in the reaction. The former afforded 36% of the final product while the latter yielded 69%. Interestingly, the hindered 3-hydroxy-2-naphthoic acid **5.1d** reacted efficiently with both DMAD and ethyl propiolate with good conversion. However, with thiosalicylic acid **5.1e**, conversion was moderate with DMAD and very low with methyl propiolate.



a) All reactions were carried out in a Schlenk tube. Reaction conditions: 1a (1.2 equiv.), alkyne (1 equiv.), $NaHCO_3$ (1.2 equiv.), CuI (1 equiv.), acetonitrile (2 ml), 24 h, 80°C. Isolated yield after column chromatography is reported.

Table 5.4 Isolated benzodioxinone derivatives with yield

The final structure of the compound was unequivocally confirmed by taking the single-crystal X-ray crystallographic data of the derivative **5.3da**.

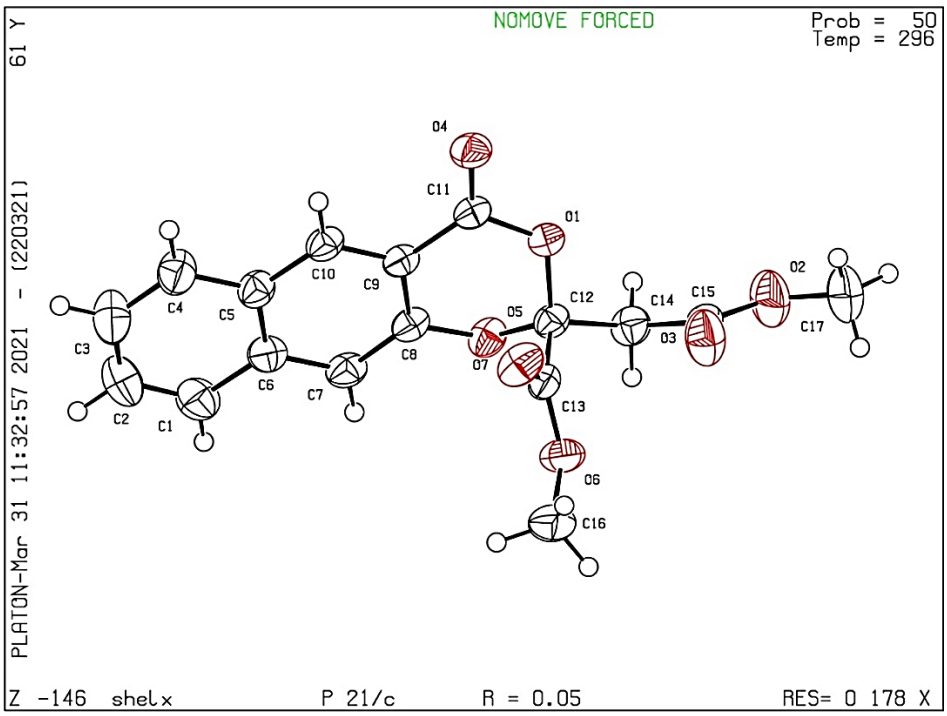
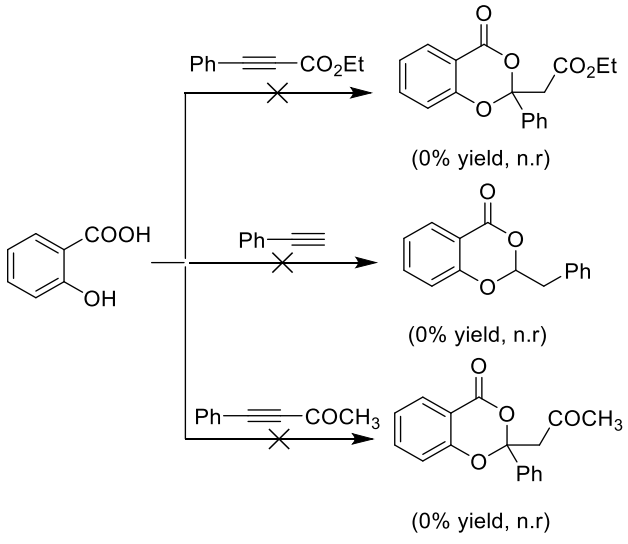


Figure 5.5 ORTEP diagram obtained for **5.3da**

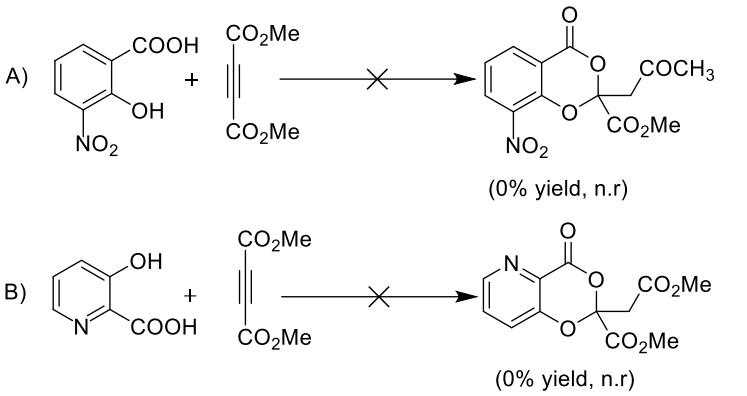
However, when sterically hindered alkynes such as ethyl phenylpropiolate, acetylenic ketone and phenylacetylene were incorporated in the reaction, no expected product was formed (**Scheme 5.2**).



Condition: CuI (1 equiv.), $NaHCO_3$ (1.2 equiv.), CH_3CN (2 ml), 80°C, 24h

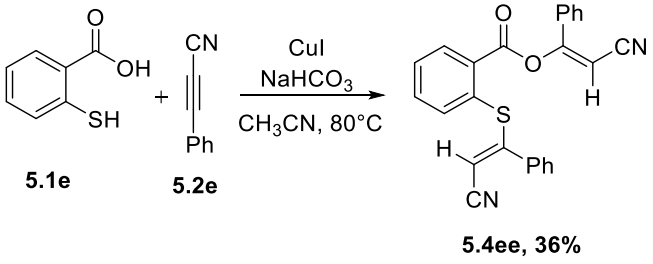
Scheme 5.2

Similarly, electron deficient 2-hydroxy-3-nitrobenzoic acid and 3-hydroxypicolinic acid were not successful in the reaction as the former yielded a sluggish reaction mixture while the latter didn't react at all.



Scheme 5.3

Surprisingly, an unexpected reactivity was observed when thiosalicylic acid was treated with 3-phenylpropiolonitrile **5.2e** under the optimized reaction conditions. Contrary to the expected 1,3-benzothiinone, the 1:2 adduct 2-cyano-1-phenylvinyl(2-(2-cyano-1,2-diphenylvinyl)-thio)benzoate (**5.4ee**) was obtained as the final product (**Scheme 5.4**).



Scheme 5.4

The final structure of the compound **5.4ee** was then verified from the spectral techniques available. The unique absorption band at 2216 cm^{-1} of the IR spectrum corresponds to the –CN functionality present in the compound (**Figure 5.6**). $C{=}O_{str}$ frequency is observed at 1739 cm^{-1}. In the ^{1}H NMR spectrum of the compound, the two protons of the olefinic bonds appear as two singlets at δ= 5.83 and 5.78 ppm (**Figure 5.7**). The carbon atoms of the nitrile groups exhibit the signals at δ= 116.2 and 114.6 ppm. All the other carbon atoms resonate in the range of δ=164.3- 87.7 ppm (**Figure 5.8**). The mass obtained from HR-MS is in good agreement with the expected mass of the compound (**Figure 5.9**).

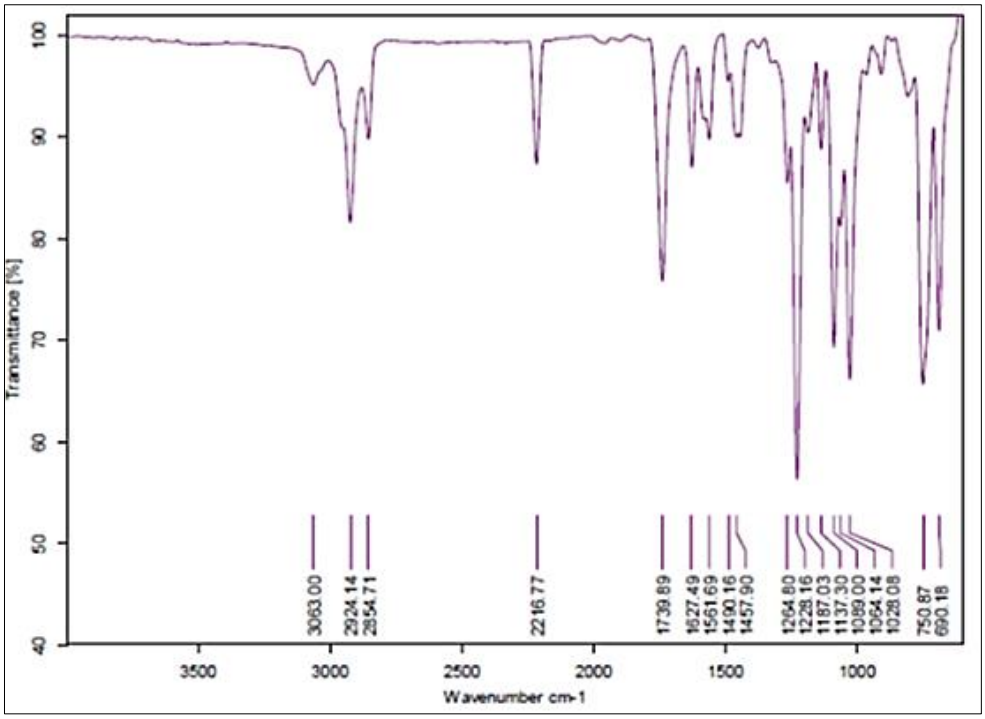


Figure 5.6 FTIR spectrum of **5.4ee**

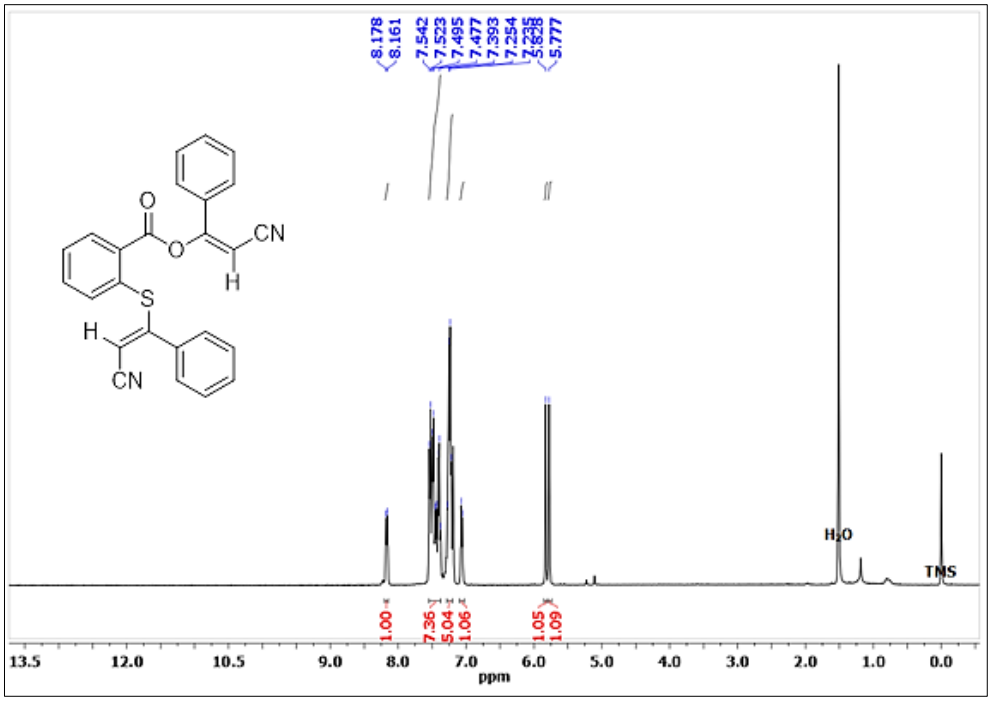


Figure 5.7 ^{1}H NMR spectrum of **5.4ee**

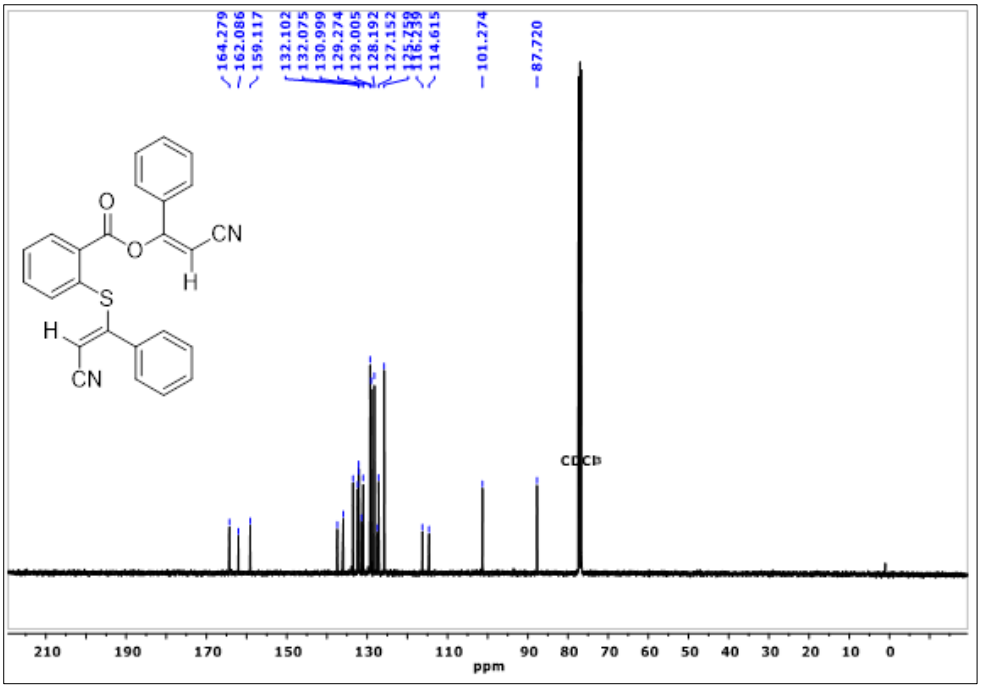


Figure 5.8 ^{13}C NMR spectrum of **5.4ee**

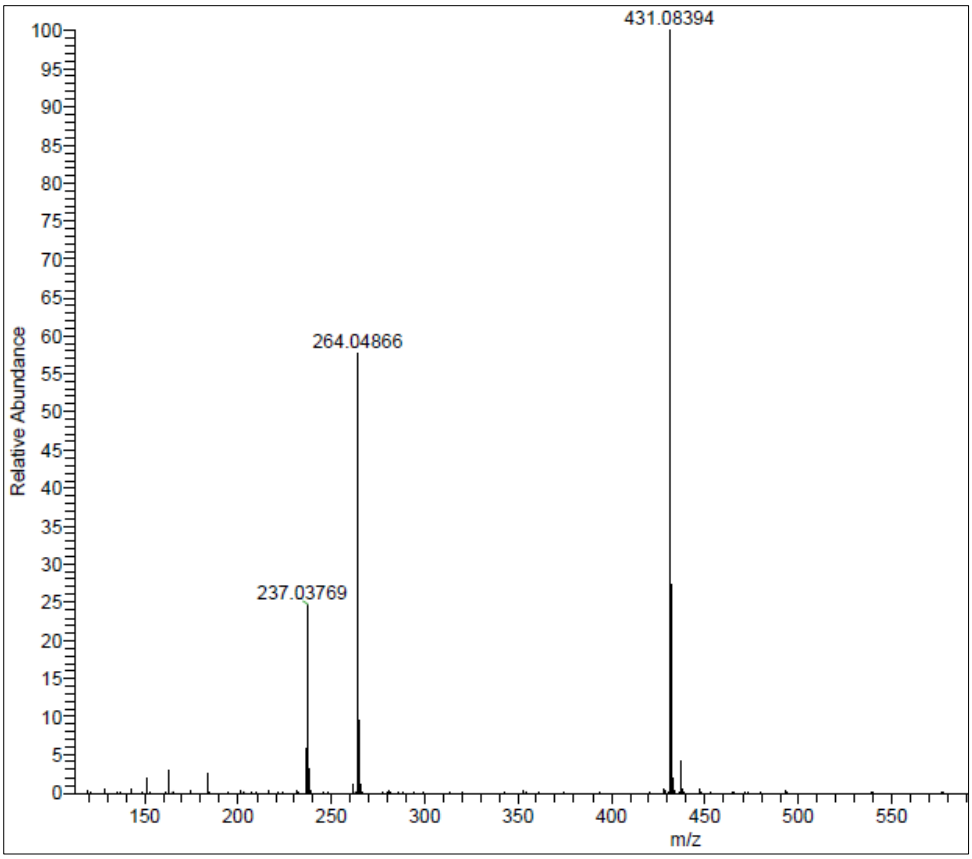
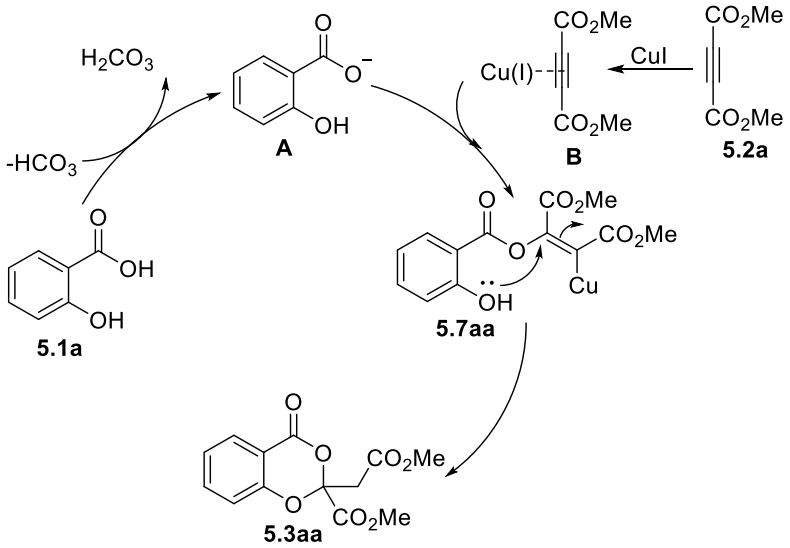


Figure 5.9 HRMS spectrum of **5.4ee**

5.5 PLAUSIBLE MECHANISM OF THE REACTION

A plausible reaction mechanism is shown in **Scheme 5.5** based on the control experiments conducted. The initial event is the acid deprotonation of **5.1a** by the base (Liang et al. 2020; Xu et al. 2018). The carboxylate then adds to the Cu(I) coordinated alkyne to afford the linear adduct **5.7aa**, which was isolated, characterized, and compared with the literature reports.



Scheme 5.5

When the reaction was repeated at room temperature, we could exclusively isolate the intermediate **5.7aa**, and the structure of the intermediate was confirmed by analysing the ^{1}H and ^{13}C NMR. The –OH proton exhibits a peak at δ= 9.97 ppm and the olefinic proton at δ= 6.80 ppm, which confirms the linear structure of the adduct **5.7aa.** The six $–OCH_3$ protons appear at δ= 3.86 and δ= 3.72 ppm as singlets. All the aromatic protons resonate from the region of δ= 6.93 -7.99 ppm (**Figure 5.10**). In the ^{13}C NMR spectrum $–OCH_3$ carbon atoms shows peaks at δ=53.5 and 52.4 ppm. Carbonyl carbon atoms appear at δ= 167.2 and 163.1 ppm. All the aromatic carbons were also present in the expected range (**Figure 5.11**).

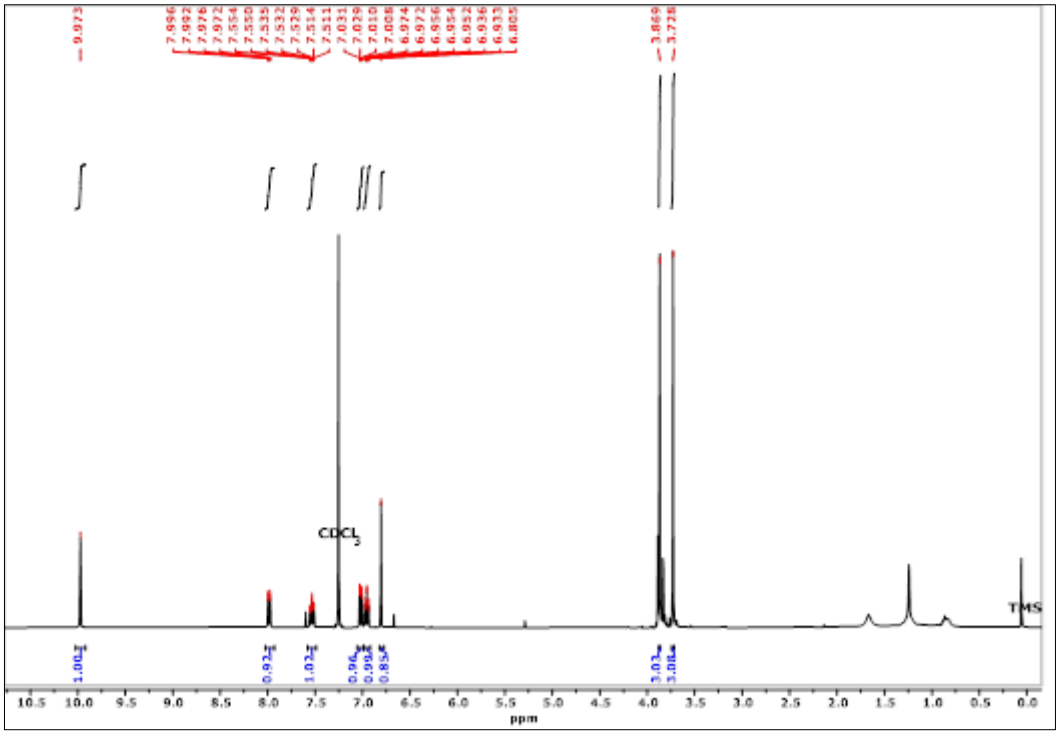


Figure 5.10 ^{1}H NMR spectrum of **5.7aa**

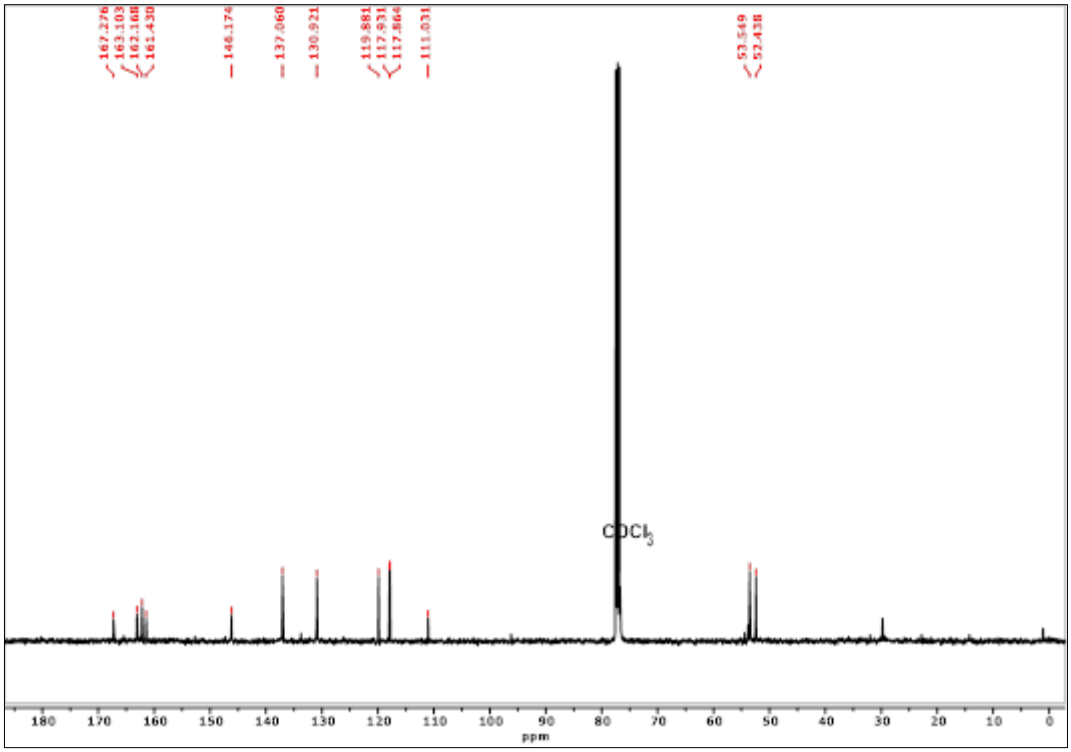


Figure 5.11 ^{13}C NMR spectrum of **5.7aa**

5.6 SYNTHETIC TRANSFORMATIONS OF BENZO [1,3]DIOXIN-4-ONES

5.6.1 Synthesis of salicylamide derivatives from benzo [1,3]dioxin-4-ones

The 4H-benzo[d][1,3]dioxin-4-one derivatives are widely used in synthetic organic chemistry as a versatile synthetic intermediate. A spectrum of compounds such as amide, ester, alcohol, aldehyde etc., can be easily accessed from the 1,3-benzodioxinone derivatives (Bajwa and Jennings 2006; Soltani and De Brabander 2005). We were particularly interested in their conversion to amides because salicylamides are widely used in medicinal chemistry as various receptor inhibitors (Balan et al. 2012; Combrink et al. 2000). Because of their antimicrobial and tuberculostatic activity, salicylamide has attracted synthetic organic chemists' attention for a long time (Burgart et al. 2020; Lagoja and De Clercq 2008; Pauk et al. 2013).

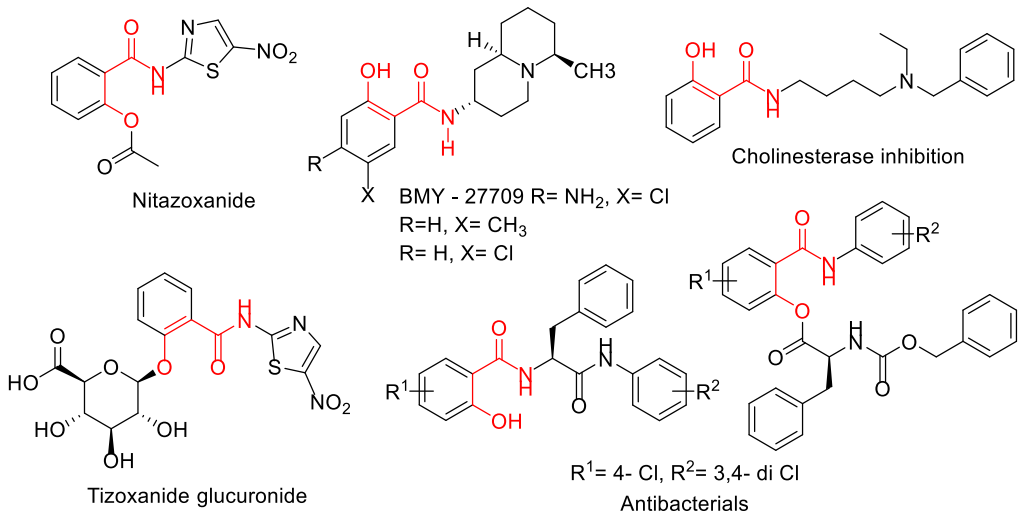
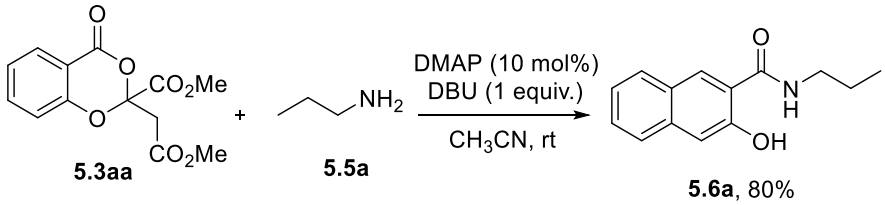


Figure 5.12 Biologically important salicylamide derivatives

Considering the biological importance of the salicylamide derivatives, we treated the final 1,3-benzodioxinones with various amines expecting easy access to salicylamides. Following the literature procedure of amide synthesis (Yang and Birman 2009), we treated **5.3aa** and n-propylamine **5.5a** in the presence of DMAP (10 mol%) and DBU (1 equiv.) in acetonitrile at room temperature for 8 h.



Scheme 5.6

The salicylamide derivative **5.6a** obtained was characterized using FTIR, ^{1}H NMR, ^{13}C NMR and mass spectrometry. The FTIR spectrum of the derivative **5.6a** is shown in **Figure 5.12**. All the aromatic protons of the compound appear in the ^{1}H NMR spectrum from δ= 7.86- 7.22 ppm. The hydroxyl proton resonates at δ= 11.73 ppm as a singlet. Peak at δ= 6.50 ppm corresponds to the –NH proton. The two –NCH_2- protons appear at δ= 3.42 as a quartet with a coupling constant of *J*= 7.2 Hz, and the three –CH_3 protons shows a triplet at δ= 0.97 ppm with a coupling constant *J*= 7.2 Hz (**Figure 5.13**). All the carbon atoms present in the compound was confirmed from ^{13}C spectrum. Aromatic carbon atoms present in the region of δ = 156.5 to 112.3 ppm. The carbonyl carbon atom resonates at δ = 169.7, and the three aliphatic carbon atoms appears at δ = 41.6, 22.8, and 11.5 ppm (**Figure 5.14**). The mass calculated for the compound $C_{14}H_{16}NO_2$ $[M+H]^+$ was 230.1176 which was found to be in good agreement with the obtained value 230.10.

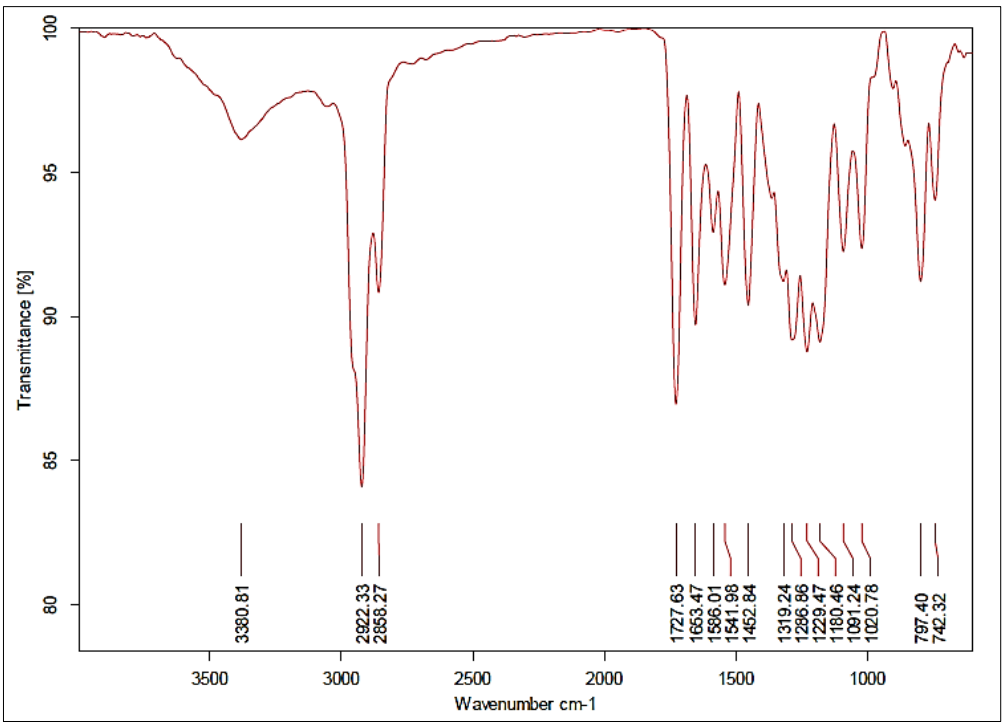


Figure 5.13 FTIR spectrum of the derivative **5.6a**

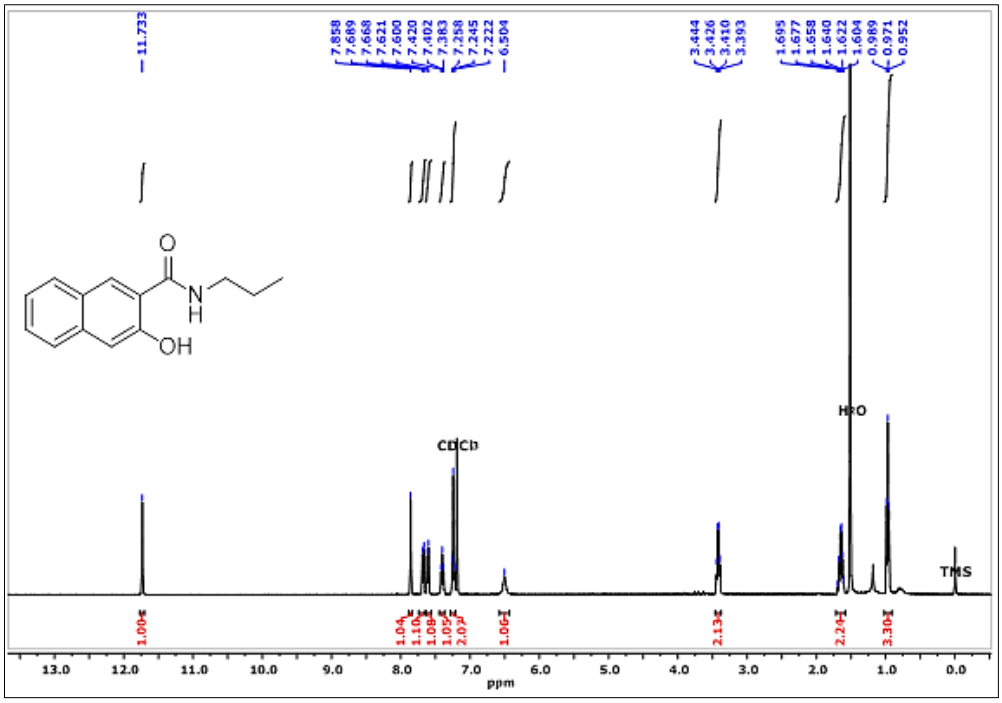


Figure 5.14 ^{1}H NMR spectrum of **5.6a**

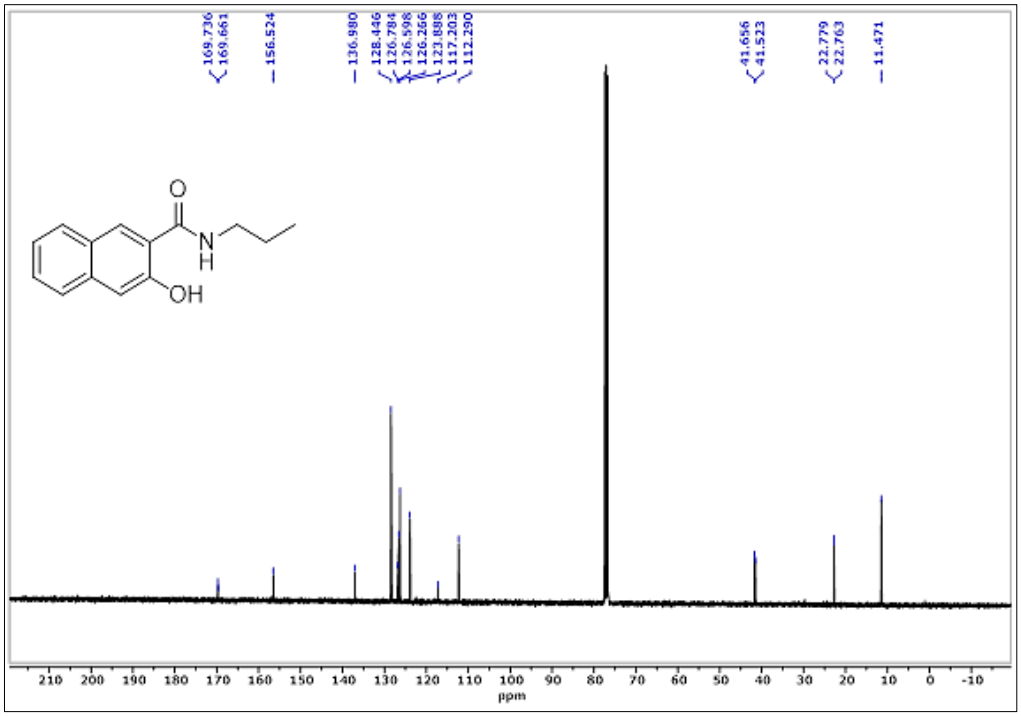


Figure 5.15 ^{13}C NMR spectrum of **5.6a**

The reaction was successful, and the expected salicylamide was formed in good yields when benzodioxinones were treated with various primary amines (**Table 5.5**). The strategy was quite versatile, and other primary amines such as isopropylamine **5.5b**, benzylamine **5.5c** and cyclohexylamine **5.5d** readily afforded the salicylamide in

moderate to good yield. Interestingly, the heterocyclic amine 2-thiophenemethylamine also resulted in the expected product **5.6e** in 43% yield. At the same time, secondary amines such as diethylamine and diphenylamine were not very effective. 1,3-Benzodioxinones derived from both salicylic acid and 3-hydroxy-2-naphthoic acid yielded the amide at room temperature. However, an attempt to perform the amide synthesis in a one-pot, two-step process, without isolating the 1,3-benzodioxinone was less effective as the amide **5.6a** was formed only in 35% yield. It is noteworthy that the previous reports on the conversion of 1,3-benzodioxinones to amide involved treating the reagents in refluxing toluene while the present methodology made it feasible at room temperature itself. However, our initial results show that the method is best suited for aliphatic primary amines as poor conversion was observed with anilines and secondary amines.

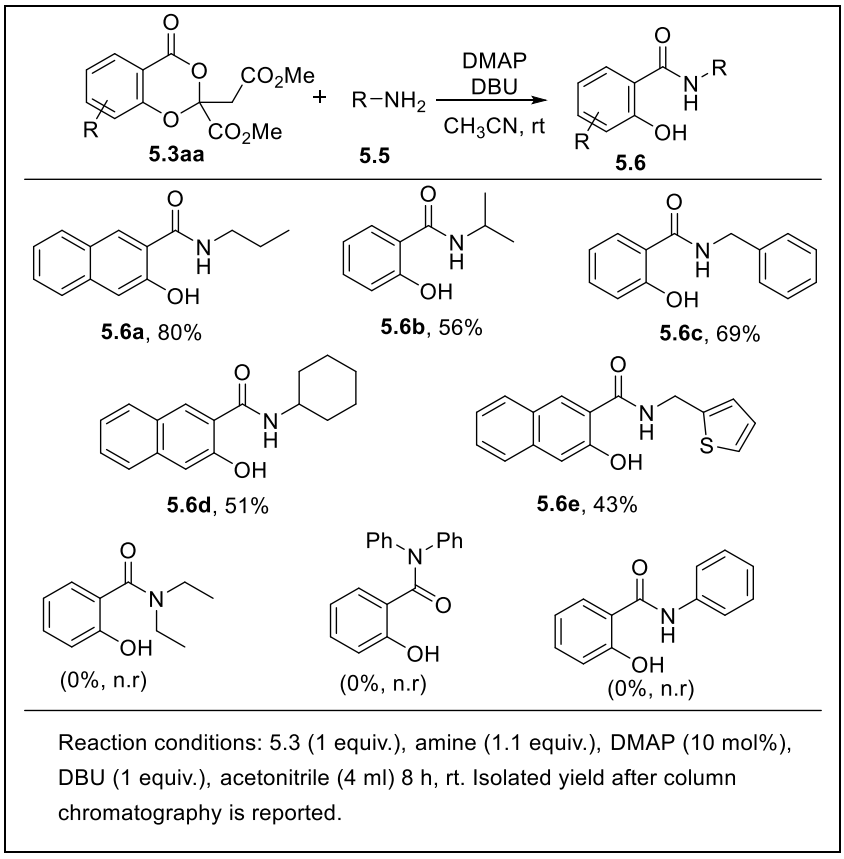
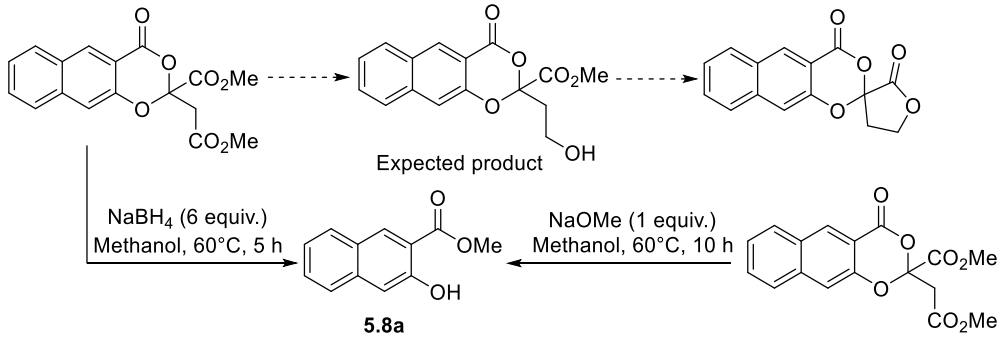


Table 5.5 Synthesis of salicylamides from 1,3-benzodioxinones

5.6.2 Reduction of benzodioxinone derivative with $NaBH_4$

An attempt was made to selectively reduce one of the ester groups of benzodioxinone derivatives. Methyl 2-(2-methoxy-2-oxoethyl)-4-oxo-4H-naphtho[2,3-d][1,3]dioxine-2-carboxylate (**5.3da**) was chosen for the reduction and the reaction was carried out in methanol at 60 °C using $NaBH_4$ (6 equiv.). The reaction was completed within 5 h and a new spot was observed in the TLC. The fraction formed was isolated and characterized. In contrary to the expectation, the product obtained was methyl 3-hydroxy-2-naphthoate (**5.8a**). To confirm, the reaction was repeated under the same condition by adding NaOMe instead of $NaBH_4$. The same fraction was formed in the reaction confirming the ring opening reaction of **5.3da** to generate 3-hydroxy-2-naphthoate (**5.8a**). The FTIR spectrum, ^{1}H NMR spectrum and ^{13}C NMR spectrum of the compound **5.8a** is shown in **Figure 5.15, Figure 5.16 and Figure 5.17** respectively.



Scheme 5.7

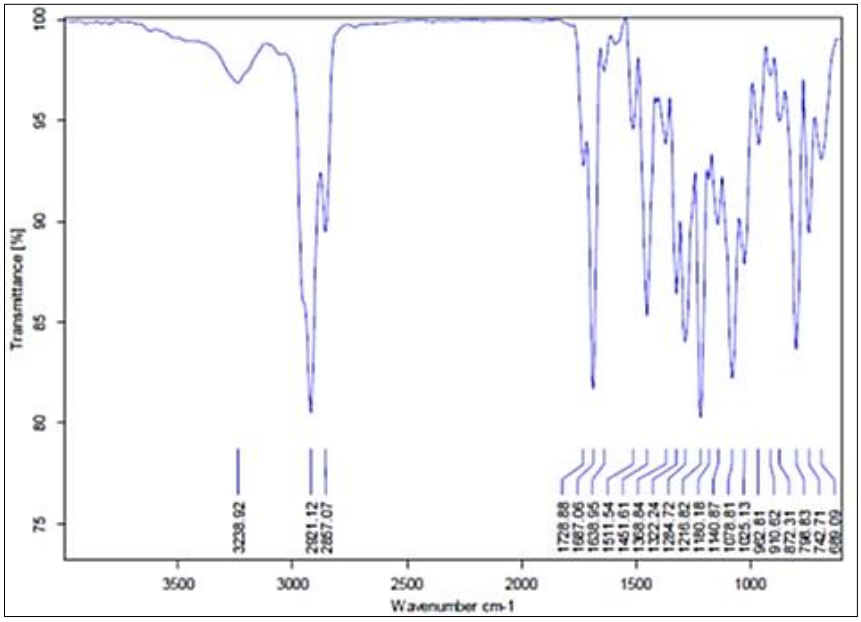


Figure 5.16 FTIR spectrum of **5.8a**

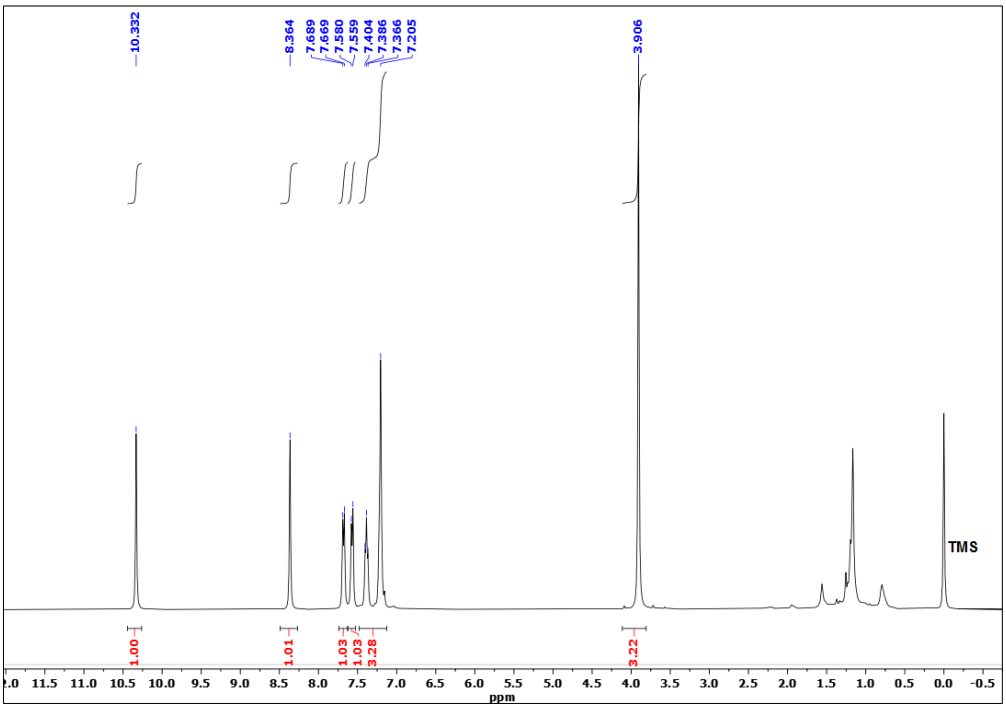


Figure 5.17 ^{1}H NMR spectrum of **5.8a**

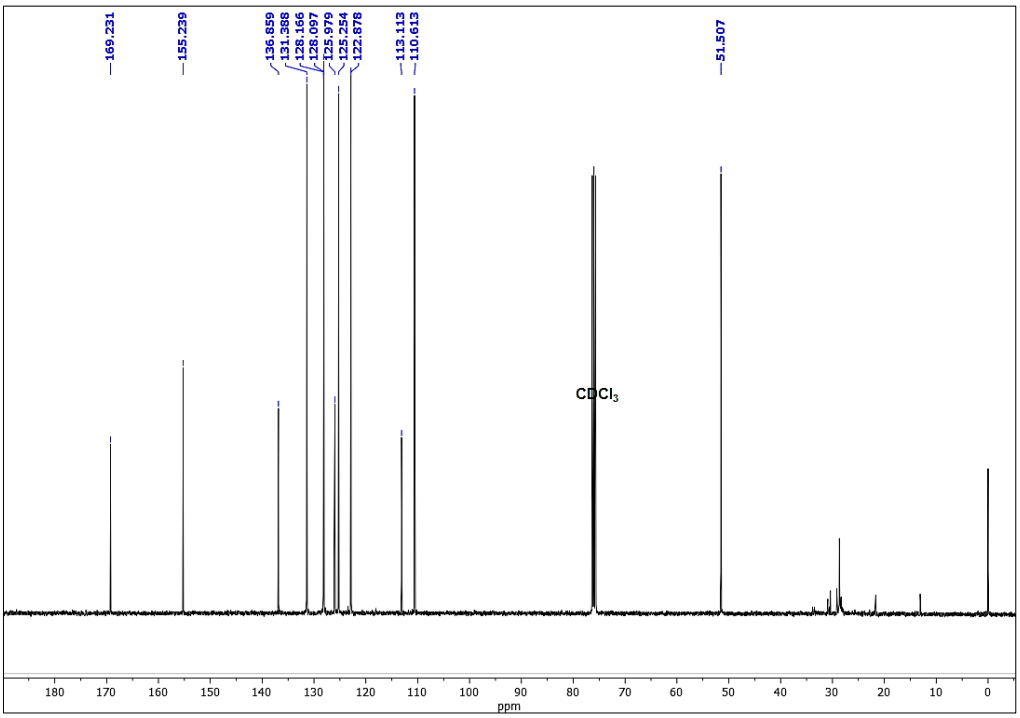


Figure 5.18^{13}C NMR spectrum of **5.8a**

5.7 CONCLUSIONS

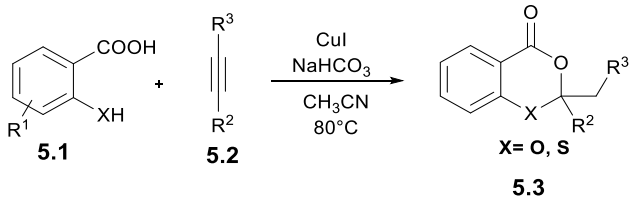
- An efficient and modified strategy for 4H-benzo[d][1,3]dioxin-4-one derivatives has been developed.
- The method involves a CuI mediated addition between salicylic acid and acetylenic esters in a basic medium followed by intramolecular cyclization.
- Disubstituted acetylenic esters such as DMAD and DEAD, and monosubstituted propionic esters-methyl propiolate and ethyl propiolate were equally effective in the reaction.
- All the derivatives synthesized was exclusively characterized and confirmed from FT-IR, ^{1}H NMR, ^{13}C NMR, Mass spectrometry and SCXRD.
- Sterically hindered alkyne, 3- phenyl propiolonitrile also effectively reacted with salicylic acid to yield 4H-benzo[d] [1,3]dioxin-4-one derivative (**5.3ae**).
- The sulphur analogue of salicylic acid- thiosalicylic acid also showed the same reactivity towards acetylenic esters and the corresponding benzothiine derivative was obtained (compound **5.3ea**) in moderate yield.
- The reaction of 3-hydroxy-2-naphthoic acid with both DMAD and ethyl propiolate resulted in polycyclic compounds, methyl-2-(2-methoxy-2-oxoethyl)-4-oxo-4H-naphtho[2,3-d][1,3]dioxine-2-carboxylate (**5.3da**) and Ethyl-2-(4-oxo-4H-naphtho[2,3-d][1,3]dioxin-2-yl)acetate (**5.3dd**) respectively.
- An unexpected reactivity was observed when thiosalicylic acid was treated with 3-phenylpropiolonitrile which yielded a 1:2 adduct 2-cyano-1-phenylvinyl(2-(2-cyano-1,2-diphenylvinyl)-thio)benzoate (**5.4ee**).
- The reaction intermediate **5.7aa** was isolated and characterized by ^{1}H NMR and ^{13}C NMR spectroscopy.
- The final structure of the 4H-benzo[d] [1,3]dioxin-4-one was exclusively confirmed from the single crystal X- ray diffraction analysis of the derivative **5.3da**.
- An efficient route for the synthetic transformation of benzodioxinones to salicylamide derivatives at room temperature was proposed and various salicylamides generated from primary amines were isolated and characterized.

5.8 EXPERIMENTAL SECTION

Unless otherwise stated, all reactions were carried out in a Schlenk tube. All the reagents were bought from commercial suppliers and used as such without additional purification. The crude reaction mixture was purified with silica gel (60‑120 mesh) column chromatography using a hexane-ethyl acetate solvent mixture as the eluent. The isolated compounds were characterized by ^{1}H and ^{13}C NMR spectroscopy, infrared spectroscopy, and high-resolution mass spectrometry (HRMS).

Melting points of the solid samples were determined using the Stuart melting point apparatus. Other characterizations such as ^{1}H NMR (400 MHz) and ^{13}C NMR spectra were recorded in $CDCl_3$/ DMSO, on Bruker Ascend^{TM} 400 MHz spectrometer and JEOL JNM- ECZ 400/L1 high-resolution multinuclear FT- NMR spectrometer with tetramethyl silane (TMS; δ H=0 ppm) as an internal standard, and chemical shifts were reported in ppm relative to TMS. The resonance multiplicity is described as s (singlet), d (doublet), t (triplet), m (multiplet), dd (doublet of doublets), and q (quartet). Infrared spectra were recorded on JASCO FTIR-4100 using ATR, and only intense peaks were reported. HRMS were recorded on a Thermo Scientific Exactive mass spectrometer using the ESI method with an orbitrap mass analyzer.

5.8.1 General procedure for the synthesis of 4*H*-benzo[d][1,3]dioxin-4-one derivatives



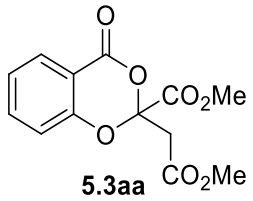
Scheme 5.8

To an oven-dried Schlenk tube equipped with a magnetic stirrer, 2- hydroxybenzoic acid (0.6 mmol, 1.2 equiv.) was added. $NaHCO_3$ (0.6 mmol, 1.2 equiv.) and CuI (0.5 mmol, 1 equiv.) were weighed and added to the Schlenk tube. Alkyne (0.5 mmol, 1 equiv.) was then added, followed by 2 ml acetonitrile solvent. The reaction vessel was then kept for stirring in an oil bath of 80 °C temperature. The progress of the reaction was monitored by TLC. After 24 hrs of reaction, the reaction mixture was diluted with ethyl acetate and was subjected to celite filtration. The filtrate was then collected and

concentrated, and the residue was purified by silica gel column chromatography using pet ether- ethyl acetate as eluent.

5.8.2 ^{1}H and ^{13}C NMR spectra of 4*H*-benzo[d][1,3]dioxin-4-one derivatives

Methyl 2-(2-methoxy-2-oxoethyl)-4-oxo-4*H*-benzo[d][1,3]dioxine-2-carboxylate (5.3aa) : Following the general procedure, the reaction between dimethyl acetylene dicarboxylate (0.5 mmol, 71.0 mg, 61.2 µl) with 2-hydroxybenzoic acid (0.6 mmol, 82.8 mg) in presence of $NaHCO_3$ (0.6 mmol, 50.4 mg) and additive CuI (0.5 mmol, 95.2 mg) in acetonitrile at 80 °C, yielded the desired product methyl 2-(2-methoxy-2-oxoethyl)-4-oxo-4*H*-benzo[d][1,3]dioxine-2-carboxylate as a white solid in 88% yield (123 mg).



5.3aa

Chemical Formula: $C_{13}H_{12}O_7$

Melting point 99- 101°C.

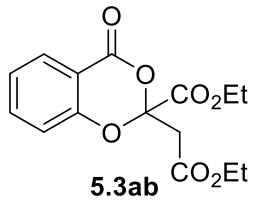
FT-IR (ATR): ν_{max}= 2957, 2922, 1757, 1612, 1509, 1467, 1440, 1366, 1302 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.88 (d, *J*= 7.2 Hz, 1H), 7.52- 7.48 (m, 1H), 7.13- 7.09 (m, 1H), 6.98 (d, J= 8.0 Hz, 1H), 3.68 (s, 6H), 3.37-3.25 (m, 2H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ = 165.9, 165.1, 158.0, 154.1, 135.7, 128.8, 122.9, 115.8, 112.8, 99.6, 52.7, 51.4, 41.2 ppm

HRMS (ESI) calcd for $C_{13}H_{12}O_7Na$ $[M+Na]^+$ 303.0475 found 303.0478.

Ethyl 2-(2-ethoxy-2-oxoethyl)-4-oxo-4*H*-benzo[d][1,3]dioxine-2-carboxylate (5.3ab): Following the general procedure, the reaction between Diethyl acetylene dicarboxylate (0.5 mmol, 85 mg, 80 µl) with 2-hydroxybenzoic acid (0.6 mmol, 82.8 mg) in presence of $NaHCO_3$ (0.6 mmol, 50.4 mg) and additive CuI (0.5 mmol, 95.2 mg) in acetonitrile at 80 °C, yielded the desired product Ethyl 2-(2-ethoxy-2-oxoethyl)-4-oxo-4*H*-benzo[d][1,3]dioxine-2-carboxylate as a viscous oily liquid in 72% yield (110.8 mg).



5.3ab

Chemical Formula: $C_{15}H_{16}O_7$

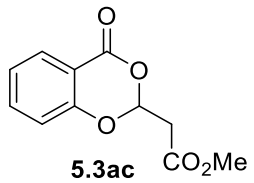
FT-IR (ATR): ν_{max}= 2989, 1739, 1610, 1472, 1382, 1300, 1190, 1075, 1013 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.87 (d, *J*= 8 Hz, 1H), 7.52-7.48 (m, 1H), 7.12- 7.08 (m, 1H), 6.98 (d, *J*= 8.4 Hz, 1H), 4.17- 4.09 (m, 4H), 3.34 (d, *J*= 15.6, 1H), 3.24 (d, *J*= 15.6, 1H), 1.21 (t, 8 Hz, 3H), 1.08 (t, *J*= 7.2 Hz, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ = 165.4, 164.5, 158.2, 154.2, 135.5, 128.7, 122.9, 115.8, 113.1, 99.6, 62.1, 60.5, 41.2, 12.9, 12.7 ppm

HRMS (ESI) calcd for $C_{15}H_{16}O_7Na$ $[M+Na]^+$ 331.0788 found 331.0800.

methyl 2-(4-oxo-4*H*-benzo[d][1,3]dioxin-2-yl)acetate (5.3ac): Following the general procedure, the reaction between methyl propiolate (0.5 mmol, 42 mg, 44.4 µl) with 2-hydroxybenzoic acid (0.6 mmol, 82.8 mg) in presence of $NaHCO_3$ (0.6 mmol, 50.4 mg) and additive CuI (0.5 mmol, 95.2 mg) in acetonitrile at 80 °C, yielded the desired product methyl 2-(4-oxo-4*H*-benzo[d][1,3]dioxin-2-yl)acetate as a thick viscous liquid in 63% yield (70.1 mg).



5.3ac

Chemical Formula: $C_{11}H_{10}O_5$

FT-IR (ATR): ν_{max}= 2954, 2922, 1739, 1612, 1586, 1472, 1339, 1401, 1302, 1232, 1200, 1129 cm^{-1}

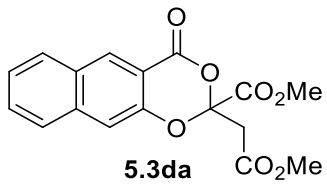
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.92 (d, *J*= 7.6, 1H), 7.53-7.50 (m, 1H), 7.15- 7.11 (m, 1H), 6.99 (d, *J*= 8 Hz, 1H), 5.98 (t, *J*= 5.6 Hz, 1 H), 3.71 (s, 3H), 3.11- 3.0 (m, 2H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ = 167.0, 160.3, 156.9, 135.4, 129.3, 122.7, 115.7, 113.3, 96.9, 51.3, 38.1 ppm

HRMS (ESI) calcd for $C_{11}H_{10}O_5Na$ $[M+Na]^+$ 245.0420 found 245.0427.

methyl 2-(2-methoxy-2-oxoethyl)-4-oxo-4*H*-naphtho[2,3-d][1,3]dioxine-2-carboxylate (5.3da): Following the general procedure, the reaction between dimethylacetylene dicarboxylate (0.5 mmol, 71 mg, 61.2 µl) with 2-hydroxynaphthoic acid (0.6 mmol, 112.8 mg) in presence of $NaHCO_3$ (0.6 mmol, 50.4 mg) and additive

CuI (0.5 mmol, 95.2 mg) in acetonitrile at 80 °C, yielded the desired product methyl 2-(2-methoxy-2-oxoethyl)-4-oxo-4*H*-naphtho[2,3-d][1,3]dioxine-2-carboxylate as a pale yellow solid in 60% yield (99 mg). Melting point 171-173°C.



5.3da

Chemical Formula: $C_{17}H_{14}O_7$

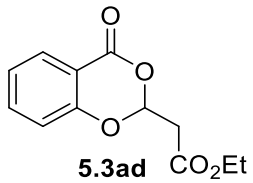
FT-IR (ATR): ν_{max}= 2956, 2922, 1749, 1636, 1607, 1302, 1246, 1193, 1069, 1010 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.52 (s, 1H), 7.84 (d, *J*= 8 Hz, 1H), 7.69 (d, *J*= 8 Hz, 1H), 7.54- 7.50 (m, 1H), 7.42- 7.34 (m, 2H), 3.69 (s, 3H), 3.64 (s, 3H), 3.41 (d, *J*= 16 Hz, 1H), 3.31 (d, *J*= 16 Hz, 1H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ = 166.1, 165.1, 158.5, 148.9, 136.4, 131.5, 128.9, 128.7, 128.6, 126.2, 124.9, 112.9, 111.7, 52.7, 51.4, 41.2 ppm

HRMS (ESI) calcd for $C_{17}H_{14}O_7Na$ $[M+Na]^+$ 353.0632 found 353.0642.

Ethyl 2-(4-oxo-4*H*-benzo[d][1,3]dioxin-2-yl)acetate (5.3ad): Following the general procedure, the reaction between ethyl propiolate (0.5 mmol, 49 mg, 50.6 µl) with 2-hydroxybenzoic acid (0.6 mmol, 82.8 mg) in presence of $NaHCO_3$ (0.6 mmol, 50.4 mg) and additive CuI (0.5 mmol, 95.2 mg) in acetonitrile at 80 °C, yielded the desired product ethyl 2-(4-oxo-4*H*-benzo[d][1,3]dioxin-2-yl)acetate as a thick viscous liquid in 73% yield (85.8 mg).



5.3ad

Chemical Formula: $C_{12}H_{12}O_5$

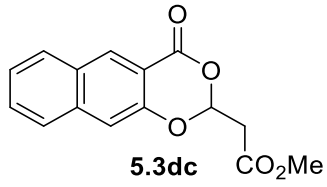
FT-IR (ATR): ν_{max}= 2926, 1738, 1612, 1586, 1472, 1411, 1302, 1234, 1186, 1129, 1023 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.91 (d, *J*= 7.6 Hz, 1H), 7.53- 7.49 (m, 1H), 7.14- 7.11 (m, 1H), 6.98 (d, *J*= 8.4 Hz, 1H), 5.98 (t, *J*= 5.6 Hz, 1H), 4.16 (q, *J*= 6.8 Hz, 2H), 3.08-2.98 (m, 2H), 1.23 (t, *J*= 7.2 Hz, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ = 166.6, 160.4, 156.9, 135.4, 129.3, 122.7, 115.7, 113.3, 97.1, 60.4, 38.4, 13.1 ppm

HRMS (ESI) calcd for $C_{12}H_{12}O_5Na$ $[M+Na]^+$ 259.0577 found 259.0587.

methyl 2-(4-oxo-4*H*-naphtho[2,3-d][1,3]dioxin-2-yl)acetate (5.3dc): Following the general procedure, the reaction between methyl propiolate (0.5 mmol, 42 mg, 44.4 µl) with 2-hydroxynaphthoic acid (0.6 mmol, 112.8 mg)) in presence of $NaHCO_3$ (0.6 mmol, 50.4 mg) and additive CuI (0.5 mmol, 95.2 mg) in acetonitrile at 80 °C, yielded the desired product methyl 2-(4-oxo-4*H*-naphtho[2,3-d][1,3]dioxin-2-yl)acetate as a white solid in 46% yield (62.8 mg).



Chemical Formula: $C_{15}H_{12}O_5$

Melting point 114-116°C.

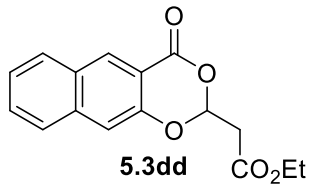
FT-IR (ATR): ν_{max}= 2956, 2922, 2853, 1742, 1636, 1607, 1577, 1505, 1347, 1247 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.56 (s, 1H), 7.86 (d, J= 8.4 Hz, 1H), 7.77 (d, J= 8 Hz, 1H), 7.56- 7.52 (m, 1H), 7.43- 7.36 (m, 2H), 6.05 (t, J= 5.2 Hz, 1H), 3.73 (s, 3H), 3.14- 3.04 (m, 2H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.2, 161.7, 152.8, 137.4, 133.0, 129.9, 129.7, 129.5, 127.2, 125.9, 114.4, 112.5, 98.3, 52.4, 39.4 ppm

HRMS (ESI) calcd for $C_{15}H_{12}O_5Na$ $[M+Na]^+$ 295.0577 found 295.0587.

Ethyl 2-(4-oxo-4*H*-naphtho[2,3-d][1,3]dioxin-2-yl)acetate (5.3dd): Following the general procedure, the reaction between ethyl propiolate (0.5 mmol, 49 mg, 50.6 µl) with 2-hydroxynaphthoic acid (0.6 mmol, 112.8 mg)) in presence of $NaHCO_3$ (0.6 mmol, 50.4 mg) and additive CuI (0.5 mmol, 95.2 mg) in acetonitrile at 80 °C, yielded the desired product ethyl 2-(4-oxo-4*H*-naphtho[2,3-d][1,3]dioxin-2-yl)acetate as a white solid in 65% yield (92.8 mg).



Chemical Formula: $C_{16}H_{14}O_5$

Melting point 106-108°C.

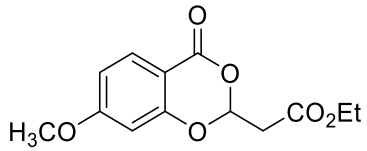
FT-IR (ATR): ν_{max}= 2923, 2860, 2853, 1735, 1635, 1575, 1505, 1475, 1346, 1188 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.56 (s, 1H), 7.86 (d, *J*= 8.4 Hz, 1H), 7.71 (d, *J*= 8.4 Hz, 1H), 7.55- 7.51 (m, 1H), 7.42- 7.36 (m, 2H), 6.05 (t, *J*= 5.2 Hz, 1H), 4.19 (dd, *J*= 6.8 Hz, 2H), 3.12- 3.02 (m, 2H), 1.25 (t, *J*= 7.6 Hz, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ = 166.7, 160.7, 151.8, 136.4, 131.9, 128.9, 128.7, 128.5, 126.1, 124.8, 113.4, 111.4, 97.4, 60.4, 38.6, 13.1 ppm

HRMS (ESI) calcd for $C_{16}H_{14}O_5Na$ $[M+Na]^+$ 309.0733 found 309.0741.

Ethyl 2-(7-methoxy-4-oxo-4*H*-benzo[d][1,3]dioxin-2-yl)acetate (5.3bd): Following the general procedure, the reaction between ethyl propiolate (0.5 mmol, 49 mg, 50.6 µl) with 2-hydroxy-4-methoxybenzoic acid (0.6 mmol, 100 mg)) in presence of $NaHCO_3$ (0.6 mmol, 50.4 mg) and additive CuI (0.5 mmol, 95.2 mg) in acetonitrile at 80 °C, yielded the desired product ethyl 2-(7-methoxy-4-oxo-4*H*-benzo[d][1,3]dioxin-2-yl)acetate as an oily liquid in 36% yield (48 mg).



5.3bd

Chemical Formula: $C_{13}H_{14}O_6$

FT-IR (ATR): ν_{max}= 2924, 2853, 1736, 1615, 1498, 1454, 1380, 12254, 1158, 1119 cm^{-1}

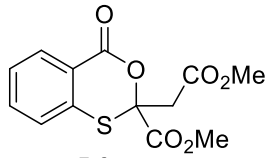
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.80 (d, J= 8.8 Hz, 1H), 6.66- 6.63 (m, 1H), 6.43 (s, 1H), 5.96 (t, 5.6 Hz, 1H), 4.16 (dd, J= 7.2 Hz, 2H), 3.78 (s, 3H), 3.05- 2.96 (m, 2H), 1.23 (t, J= 7.2 Hz, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ = 166.7, 165.2, 160.4, 158.9, 130.8, 110.6, 105.8, 99.4, 97.0, 60.3, 54.8, 38.4, 13.1 ppm

HRMS (ESI) calcd for $C_{13}H_{14}O_6Na$ $[M+Na]^+$ 289.0683 found 289.0693.

Methyl 2-(2-methoxy-2-oxoethyl)-4-oxo-4*H*-benzo[d][1,3]oxathiine-2-carboxylate (5.3ea): Following the general procedure, the reaction between dimethyl acetylene

dicarboxylate (0.5 mmol, 71 mg, 61.2 µl) with 2-mercaptobenzoic acid (0.6 mmol, 92.5 mg)) in presence of $NaHCO_3$ (0.6 mmol, 50.4 mg) and additive CuI (0.5 mmol, 95.2 mg) in acetonitrile at 80 °C, yielded the desired product methyl 2-(2-methoxy-2-oxoethyl)-4-oxo-4*H*-benzo[d][1,3]oxathiine-2-carboxylate as a white solid in 53% yield (78.4 mg).



5.3ea

Chemical Formula: $C_{13}H_{12}O_6S$

Melting point 120-122°C.

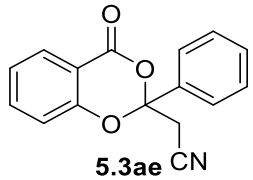
FT-IR (ATR): ν_{max}= 2955, 1735, 1438, 1403, 1283, 1204, 1139, 1061 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.13 (d, J= 7.6 Hz, 1H), 7.42- 7.38 (m, 1H), 7.28- 7.24 (m, 1H), 7.14 (d, J= 7.6 Hz, 1H), 3.69 (s, 3H), 3.65 (s, 3H), 3.32- 3.23 (m, 2H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.0, 167.3, 161.8, 133.9, 132.3, 131.8, 127.4, 127.0, 123.6, 82.9, 53.8, 52.6, 42.6 ppm.

HRMS (ESI) calcd for $C_{13}H_{12}O_6SNa$ $[M+Na]^+$ 319.0247 found 319.0261.

2-(4-oxo-2-phenyl-4*H*-benzo[d][1,3]dioxin-2-yl)acetonitrile (5.3ae): Following the general procedure, the reaction between 3-phenylpropiolonitrile (0.5 mmol, 63.5 mg) with 2-hydroxy benzoic acid (0.6 mmol, 82.8 mg)) in presence of $NaHCO_3$ (0.6 mmol, 50.4 mg) and additive CuI (0.5 mmol, 95.2 mg) in acetonitrile at 80 °C, yielded the desired product 2-(4-oxo-2-phenyl-4*H*-benzo[d][1,3]dioxin-2-yl)acetonitrile as a white solid in 55% yield (73 mg).



5.3ae

Chemical Formula: $C_{16}H_{11}NO_3$

Melting point 148-150°C.

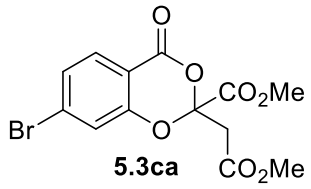
FT-IR (ATR): ν_{max}= 2954, 2923, 2255, 1749, 1612, 1590, 1479, 1466, 1450, 1302, 1089, 1028cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.74 (d, J= 7.6 Hz, 1H), 7.51- 7.47 (m, 3H), 7.32- 7.27 (m, 3H), 7.07 (d, J= 8 Hz, 1H), 6.99 (t, J= 7.6 Hz, 1H), 3.26- 3.14 (m, 2H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ = 159.4, 155.5, 136.9, 136.4, 130.4, 130.0, 129.2 (2C), 126.4 (2C), 123.7, 117.3, 114.3, 113.9, 103.5, 32.8 ppm

HRMS (ESI) calcd for $C_{16}H_{11}NO_3Na$ $[M+Na]^+$ 288.0631 found 288.0642.

methyl 7-bromo-2-(2-methoxy-2-oxoethyl)-4-oxo-4*H*-benzo[d][1,3]dioxine-2-carboxylate (5.3ca): Following the general procedure, the reaction between dimethyl acetylene dicarboxylate (0.5 mmol, 71mg, 61.2 μl) with 4-bromo-2-hydroxybenzoic acid (0.6 mmol, 130 mg)) in presence of $NaHCO_3$ (0.6 mmol, 50.4 mg) and additive CuI (0.5 mmol, 95.2 mg) in acetonitrile at 80 °C, yielded the desired product methyl methyl 7-bromo-2-(2-methoxy-2-oxoethyl)-4-oxo-4*H*-benzo[d][1,3]dioxine-2-carboxylate as a white solid in 69% yield (80 mg).



5.3ca

Chemical Formula: $C_{13}H_{11}BrO_7$

Melting point 115-117°C.

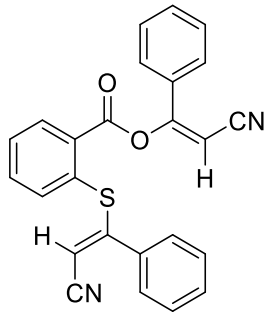
FT-IR (ATR): ν_{max}= 2956, 2921, 1757, 1602, 1578, 1423, 1367, 1307, 1273, 1169 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.73 (d, J= 8.4 Hz, 1H), 7.26- 7.19 (m, 2H), 3.71 (s, 3H), 3.69 (s, 3H), 3.36- 3.24 (m, 2H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ = 165.8, 164.6, 157.3, 154.4, 130.1, 129.8, 126.6, 119.2, 111.6, 99.8, 52.9, 51.5, 41.0 ppm

HRMS (ESI) calcd for $C_{13}H_{11}Br^{81}O_7Na$ $[(M+2)+Na]^+$ 382.9580 found 382.9573.

2-cyano-1-phenylvinyl (2-(2-cyano-1,2-diphenylvinyl)thio)benzoate (5.4ee): Following the general procedure, the reaction between 3-phenylpropiolonitrile (0.5 mmol, 63.5 mg) with 2-mercaptobenzoic acid (0.6 mmol, 92.5 mg)) in presence of $NaHCO_3$ (0.6 mmol, 50.4 mg) and additive CuI (0.5 mmol, 95.2 mg) in acetonitrile at 80 °C, yielded the product 2-cyano-1-phenylvinyl (2-(2-cyano-1,2-diphenylvinyl)thio)benzoate as a white solid in 36% yield (60 mg).



5.4ee

Chemical Formula: C25H16N2O2S

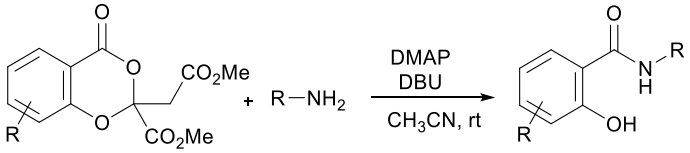
FT-IR (ATR): ν_{max}= 2924, 2854, 2216, 1739, 1627, 1561, 1490, 1457, 1264, 1228, 1187, 1137 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.17 (d, J= 6.8 Hz, 1H), 7.54- 7.37 (m, 7H), 7.28- 7.22 (m, 5H), 7.063 (d, J= 7.2 Hz, 1H), 5.83 (s, 1H), 5.78 (s, 1H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ = 164.3, 162.1, 159.1, 137.4, 135.9, 133.5, 132.4, 132.1 (2C), 131.4, 131.0, 129.3 (2C), 129.0 (2C), 128.2 (2C), 127.4, 127.2, 125.8 (2C), 116.2, 114.6, 101.3, 87.7 ppm

HRMS (ESI) calcd for $C_{25}H_{16}N_2O_2SNa$ $[M+Na]^+$ 431.0825 found 431.0839.

5.8.3 General procedure for the synthesis of salicylamide derivatives from 4*H*-benzo[d][1,3]dioxin-4-ones



5.3 5.5 5.6

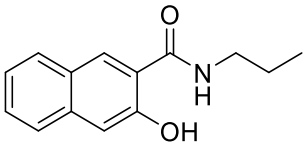
Scheme 5.9

To a 25 ml round bottom flask 0.2 mmol of 4*H*-benzo[d][1,3]dioxin-4-one derivative was added along with 10 mol% DMAP and 1 equiv. DBU in 4 ml acetonitrile. The mixture was kept for stirring at room temperature and to the stirring solution, 1.1 equiv. amine was added drop-wise. The progress of the reaction was monitored using TLC. After the completion of the reaction, acetonitrile was evaporated off under reduced pressure. The reaction mixture was subjected to column chromatography using 100-200 mesh-sized silica as the stationary phase and petether-ethyl acetate mixture as the eluent.

5.8.4 ^{1}H and ^{13}C NMR spectral data and images of salicylamide derivatives

Synthesis of 3-hydroxy-N-propyl-2-naphthamide (5.6a): To a 25 ml round bottom flask methyl 2-(2-methoxy-2-oxoethyl)-4-oxo-4H-naphtho[2,3-d][1,3]dioxine-2-

carboxylate (0.2 mmol, 66 mg) was added along with DMAP (10 mol%, 2 mg) and DBU (0.2 mmol, 30 mg) in 4 ml acetonitrile. The mixture was kept for stirring at room temperature, and to the stirring solution, n- propylamine (0.22 mmol, 13 mg, 18.1 μl) was added drop-wise. The progress of the reaction was monitored using TLC. After 8 hrs of reaction, acetonitrile was evaporated off under reduced pressure. The reaction mixture was subjected to column chromatography using 100-200 mesh-sized silica as the stationary phase and petether-ethyl acetate mixture as the eluent. The product 3-hydroxy-N-propyl-2-naphthamide was obtained as a pale-yellow solid in 80% (37 mg).



5.6a

Chemical Formula: $C_{14}H_{15}NO_2$

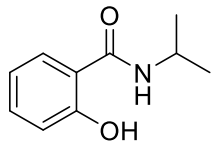
FT-IR (ATR): ν_{max}= 3380, 2922, 2858, 1727, 1653, 1586, 1541, 1452 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ = 11.73 (s, 1H), 7.86 (s, 1H), 7.68 (d, *J*= 8.4 Hz, 1H), 7.61 (d, *J*= 8.4 Hz, 1H), 7.40 (t, *J*= 7.2 Hz, 1H), 7.26- 7.22 (m, 2H), 6.50 (s, 1H), 3.42 (q, *J*= 7.2 Hz, 2H), 1.69- 1.60 (m, 2H), 0.97 (t, *J*= 7.2 Hz, 3H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ = 169.7, 156.5, 137.0, 128.4 (2C), 126.8, 126.6, 126.3, 123.9, 117.2, 112.3, 41.6, 22.8, 11.5 ppm.

Exact Mass: 229.11; LC- MS obtained: 228.10 (M-1).

Synthesis of 2-hydroxy-N-isopropylbenzamide (5.6b): To a 25 ml round bottom flask methyl 2-(2-methoxy-2-oxoethyl)-4-oxo-4H-benzo[d][1,3]dioxine-2-carboxylate (0.2 mmol, 56 mg) was added along with DMAP (10 mol%, 2 mg) and DBU (0.2 mmol, 30 mg) in 4 ml acetonitrile. The mixture was kept for stirring at room temperature, and to the stirring solution, Isopropylamine (0.22 mmol, 13 mg, 18.0 μl) was added drop-wise. The progress of the reaction was monitored using TLC. After 8 hrs of reaction, acetonitrile was evaporated off under reduced pressure. The reaction mixture was subjected to column chromatography using 100-200 mesh-sized silica as the stationary phase and pet ether-ethyl acetate mixture as the eluent. The product 2-hydroxy-N-isopropylbenzamide was obtained as a colourless oily liquid in 56% (21 mg).



5.6b

Chemical Formula: $C_{10}H_{13}NO_2$

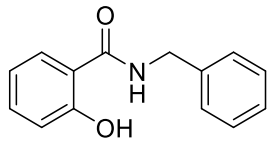
FT-IR (ATR): ν_{max}= 3370, 2974, 2927, 2861, 1636, 1591, 1539, 1496, 1455, 1366, 1299 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ = 12.46 (s, 1H), 7.38- 7.32 (m, 2H), 6.97- 6.94 (m, 1H), 6.83- 6.79 (m, 1H), 6.19 (s, 1H), 4.31- 4.22 (m, 1H), 1.26 (d, *J*= 6.4 Hz, 6H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ = 169.3, 161.6, 134.1, 125.3, 118.6 (2C), 114.5, 41.9, 22.7 (2C) ppm.

Exact Mass: 179.09; LC- MS obtained: 180.05 (M+1).

Synthesis of N-benzyl-2-hydroxybenzamide (5.6c): To a 25 ml round bottom flask methyl 2-(2-methoxy-2-oxoethyl)-4-oxo-4H-benzo[d][1,3]dioxine-2-carboxylate (0.2 mmol, 56 mg) was added along with DMAP (10 mol%, 2 mg) and DBU (0.2 mmol, 30 mg) in 4 ml acetonitrile. The mixture was kept for stirring at room temperature, and to the stirring solution, Benzylamine (0.22 mmol, 23.5 mg, 24.0 µl) was added drop-wise. The progress of the reaction was monitored using TLC. After 8 hrs of reaction, acetonitrile was evaporated off under reduced pressure. The reaction mixture was subjected to column chromatography using 100-200 mesh-sized silica as the stationary phase and petether - ethyl acetate mixture as the eluent. The product N-benzyl-2-hydroxybenzamide was obtained as a white solid in 69% (31 mg).



5.6c

Chemical Formula: $C_{14}H_{13}NO_2$

FT-IR (ATR): ν_{max}= 3370, 3034, 2922, 2854, 1729, 1637, 1594, 1539, 1237 cm^{-1}

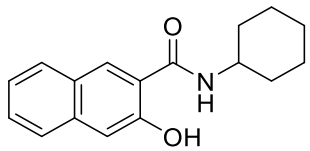
^{1}H NMR (400 MHz, $CDCl_3$) δ = 12.32 (s, 1H), 7.41- 7.29 (m, 6H), 7.25 (m, 1H), 6.99 (d, J= 8.4 Hz, 1H), 6.84- 6.80 (m, 1H), 6.61 (s, 1H), 4.63 (d, J= 6 Hz, 2H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ = 169.9, 161.7, 137.5, 134.5,129.0 (2C), 128.0 (3C), 125.4, 118.8 (2C), 114.2, 43.8 ppm.

Exact Mass: 228.09; LC- MS obtained: 228.05 (M+1).

Synthesis of N-cyclohexyl-3-hydroxy-2-naphthamide (5.6d): To a 25 ml round bottom flask methyl 2-(2-methoxy-2-oxoethyl)-4-oxo-4H-naphtho[2,3-d][1,3]dioxine-2-carboxylate (0.25 mmol, 82.6 mg) was added along with DMAP (10 mol%, 3 mg)

and DBU (0.25 mmol, 38 mg) in 4 ml acetonitrile. The mixture was kept for stirring at room temperature, and to the stirring solution, Cyclohexylamine (0.275 mmol, 27.3 mg, 31.5 µl) was added drop-wise. The progress of the reaction was monitored using TLC. After 10 hrs of reaction, acetonitrile was evaporated off under reduced pressure. The reaction mixture was subjected to column chromatography using 100-200 mesh-sized silica as the stationary phase and petether-ethyl acetate mixture as the eluent. The product N-cyclohexyl-3-hydroxy-2-naphthamide was obtained as a pale-yellow solid in 51% (34 mg).



5.6d

Chemical Formula: $C_{17}H_{19}NO_2$

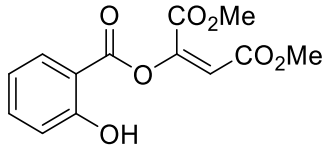
FT-IR (ATR): ν_{max}= 3351, 3056, 2928, 2855, 1710, 1580, 1533, 1453, 1305, 1226 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) δ = 11.89 (s, 1H), 7.91 (s, 1H), 7.72 (d, *J*= 8.4 Hz, 1H), 7.65 (d, *J*= 8.4 Hz, 1H), 7.47- 7.43 (m, 1H), 7.30- 7.26 (m, 2H), 6.44 (s, 1H), 4.05- 3.96 (m, 1H), 2.09- 2.04 (m 2H), 1.82- 1.65 (m, 4H), 1.49- 1.19 (m, 4H) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ = 169.0, 156.9, 137.0, 128.5, 128.48, 126.8, 126.6, 126.3, 123.9, 117.4, 112.4, 49.1, 33.1 (2C), 25.5, 24.9 (2C) ppm.

Exact Mass: 269.14; LC- MS obtained: 270.05 (M+1)

5.8.5 ^{1}H and ^{13}C NMR spectral data of isolated intermediate dimethyl 2-((2 hydroxybenzoyl)oxy)maleate



Chemical Formula: $C_{13}H_{12}O_7$

^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.97 (s, 1H), 7.99- 7.97 (m, 1H), 7.55- 7.51 (m, 1H), 7.03- 7.00 (m, 1H), 6.97- 6.93 (m, 1H), 6.80 (s, 1H), 3.86 (s, 3H), 3.72 (s, 3H) ppm

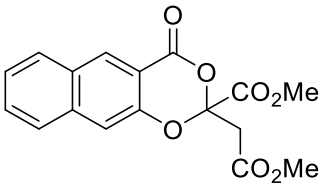
^{13}C NMR (100 MHz, $CDCl_3$) δ = 167.3, 163.1, 162.1, 161.4, 146.2, 137.1, 130.9, 119.9, 117.9, 117.86, 111.0, 53.5, 52.4 ppm.

The NMR data of the intermediate obtained is in good agreement with the NMR data repprted by Ming-Jin Fan et al. given below (Fan et al. 2006).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.99 (s, 1H), 6.94– 8.01 (m, 4H), 6.82 (s, 1H), 3.88 (s, 3H), 3.74 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ =167.1, 162.9, 162.0, 161.3, 146.0, 136.9, 130.8, 119.7, 117.8, 110.9, 53.4, 52.3.

5.8.6 Single Crystal X-ray Data of the Compound 5.*3da*

Compound 5.3da



CCDC No: 2084126

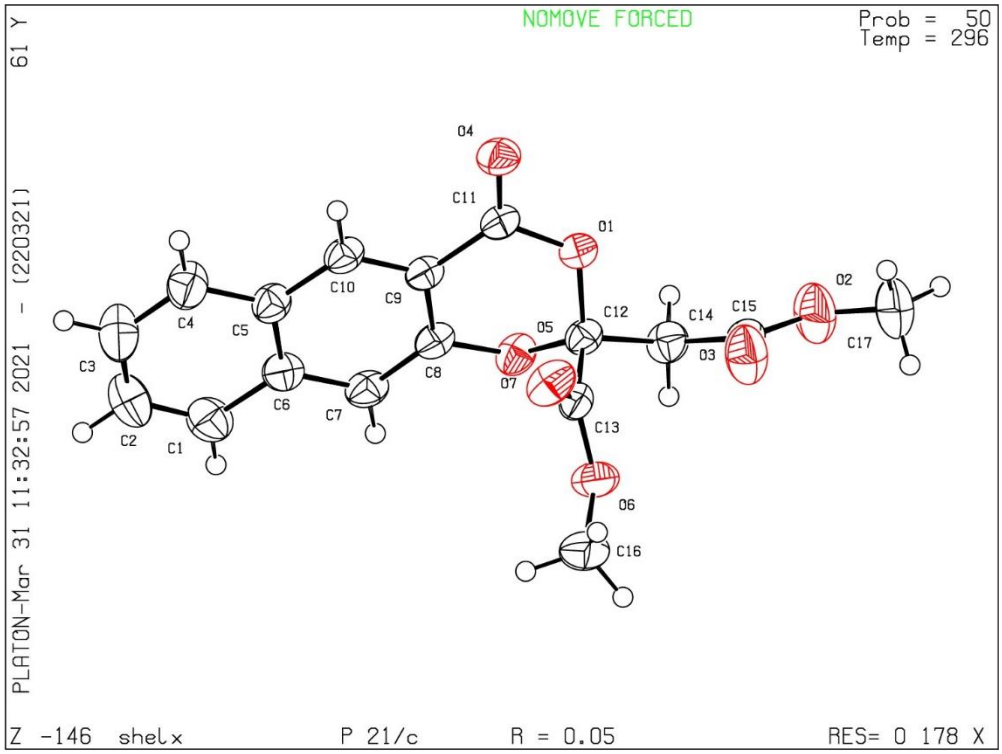


Figure 5.19 ORTEP diagram of **5.3da**

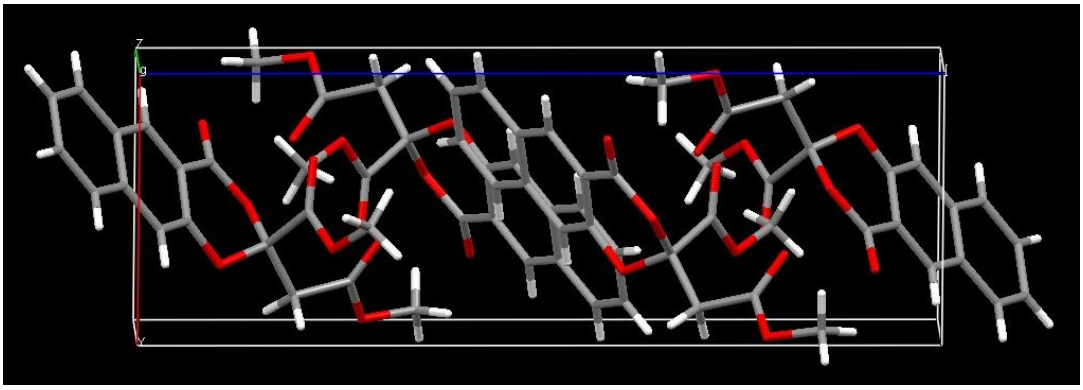


Figure 5.20 Crystal packing of **5.3da**

Crystal data and structure refinement for Compound *3da* – CCDC No: 2084126

Identification code	shelx
Empirical formula	C_{17} H_{14} O_7
Formula weight	330.28
Temperature	296(2) K
Wavelength	0.71073 Å
Crystal system, space group	Monoclinic, P 21/c
Unit cell dimensions	a = 6.2678(7) Å alpha = 90 deg.
	b = 13.2735(14) Å beta = 90.548(4) deg.
	c = 18.564(2) Å gamma = 90 deg.
Volume	1544.4(3) $Å^3$
Z, Calculated density	4, 1.420 mg/m^3
Absorption coefficient	0.112 mm^{-1}
F(000)	688
Crystal size	0.350 x 0.350 x 0.300 mm
Theta range for data collection	2.194 to 28.463 deg.
Limiting indices	-7<=h<=8, -15<=k<=17, -23<=l<=24
Reflections collected / unique	12619 / 3793 [R(int) = 0.0272]
Completeness to theta = 25.242	99.7 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.967 and 0.962
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3793 / 0 / 219

Goodness-of-fit on F^2	0.974
Final R indices [I>2sigma(I)]	R1 = 0.0463, wR2 = 0.1311
R indices (all data)	R1 = 0.0658, wR2 = 0.1492
Extinction coefficient	n/a
Largest diff. peak and hole	0.223 and -0.253 e.A^-3

Appendix IV

Representative spectra of some of the final compounds are shown:

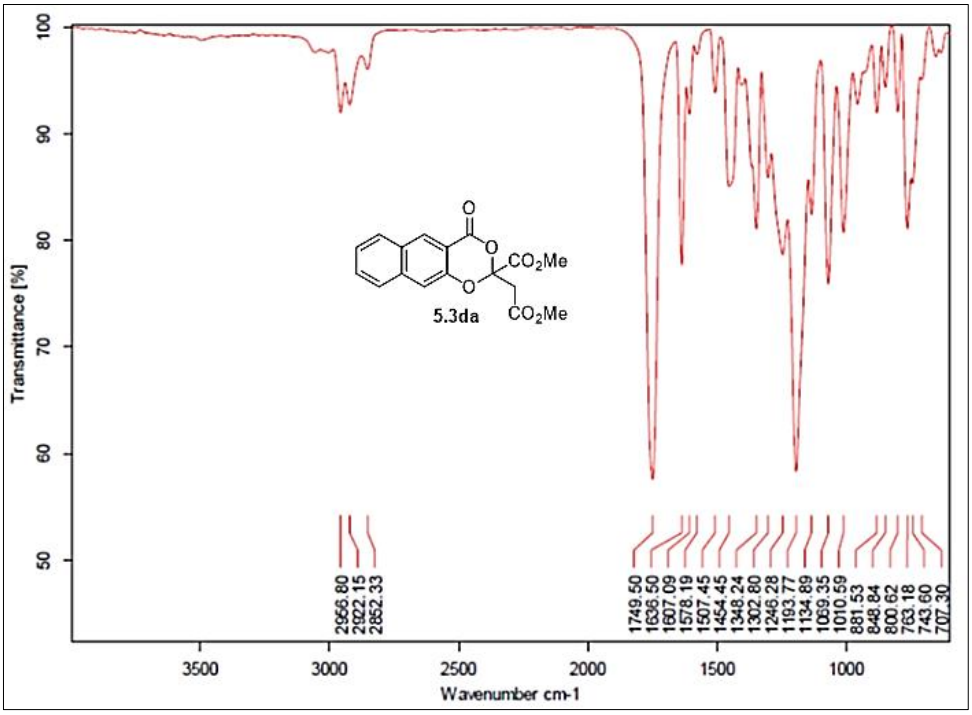


Figure 5.21 FTIR spectrum of **5.3da**

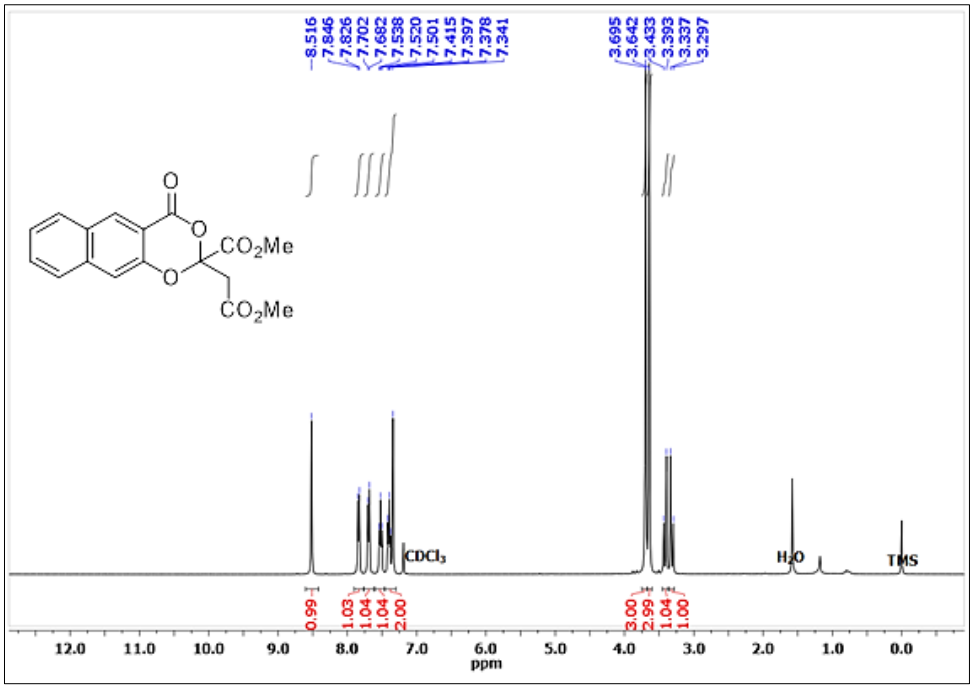


Figure 5.22 ^{1}H NMR spectrum of **5.3da**

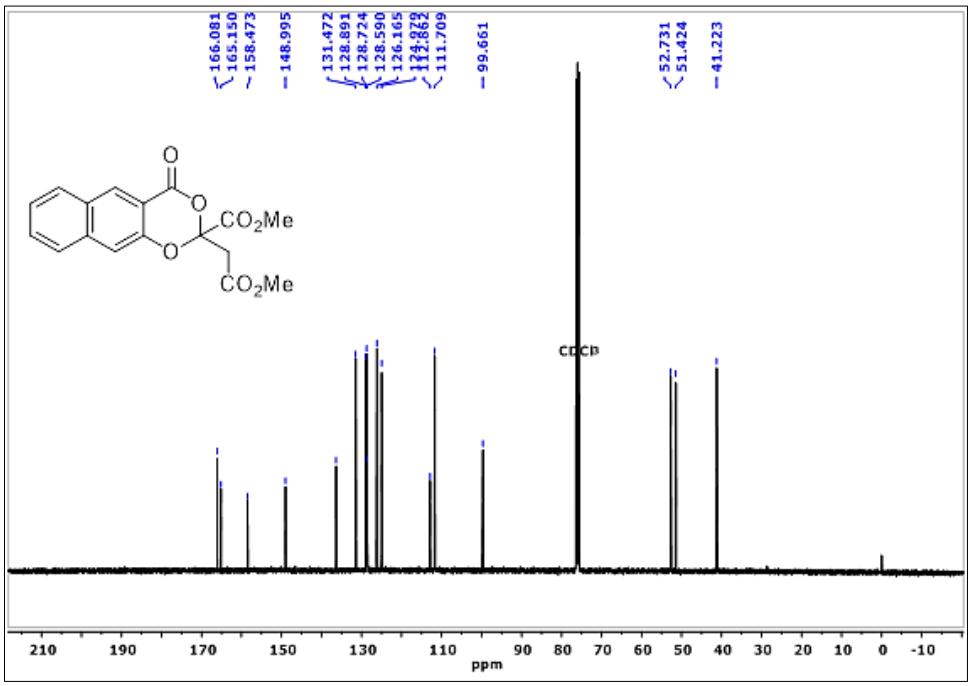


Figure 5.23 ^{13}C NMR spectrum of **5.3da**

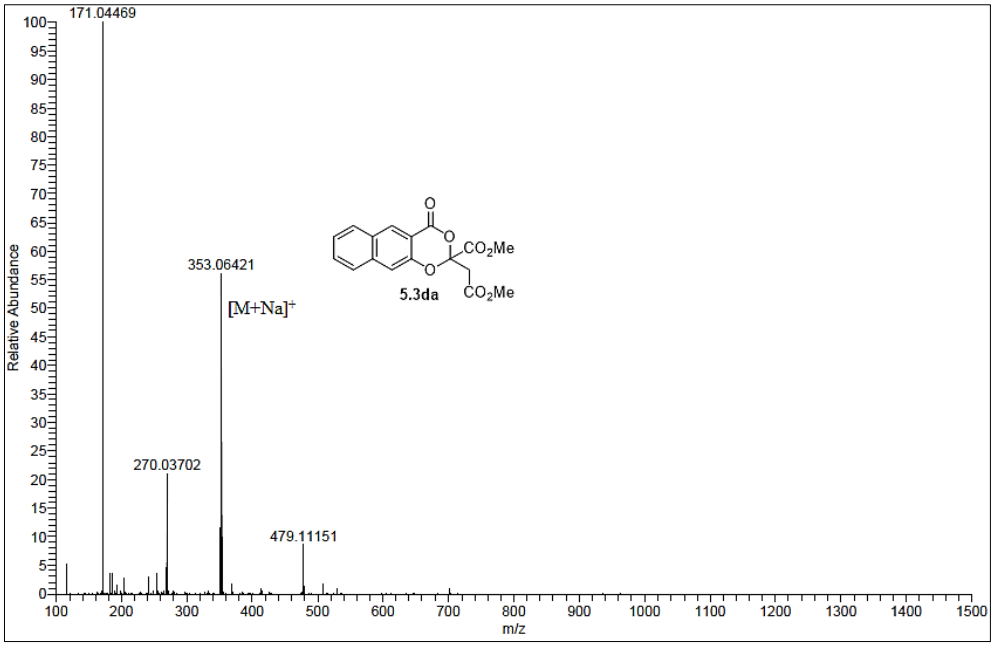


Figure 5.24 HRMS spectrum of **5.3da**

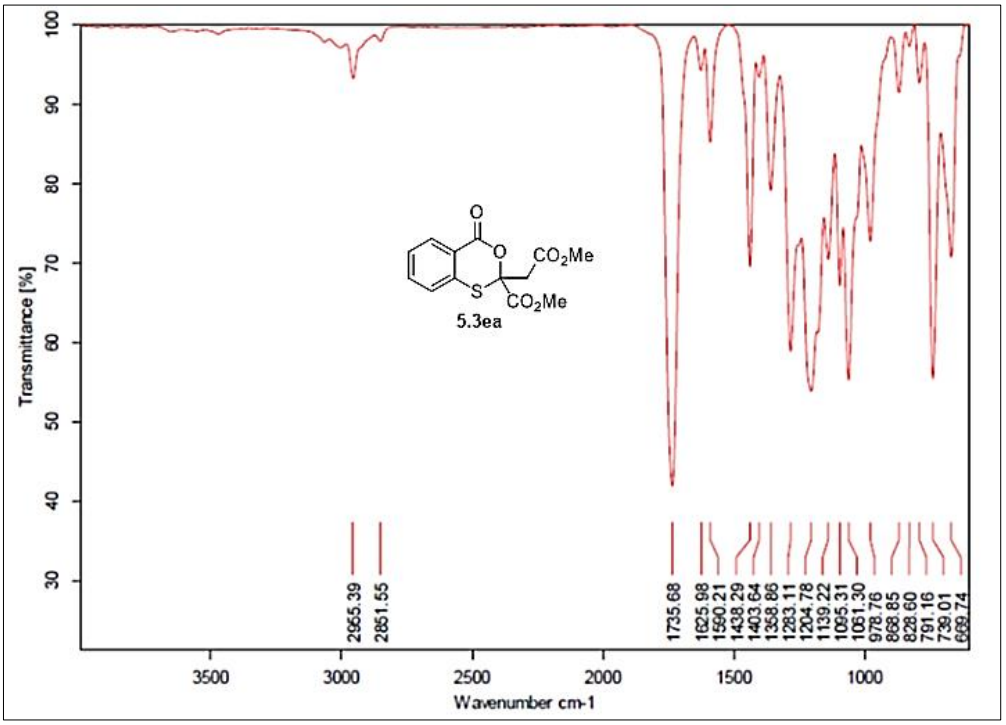


Figure 5.25 FTIR spectrum of **5.3ea**

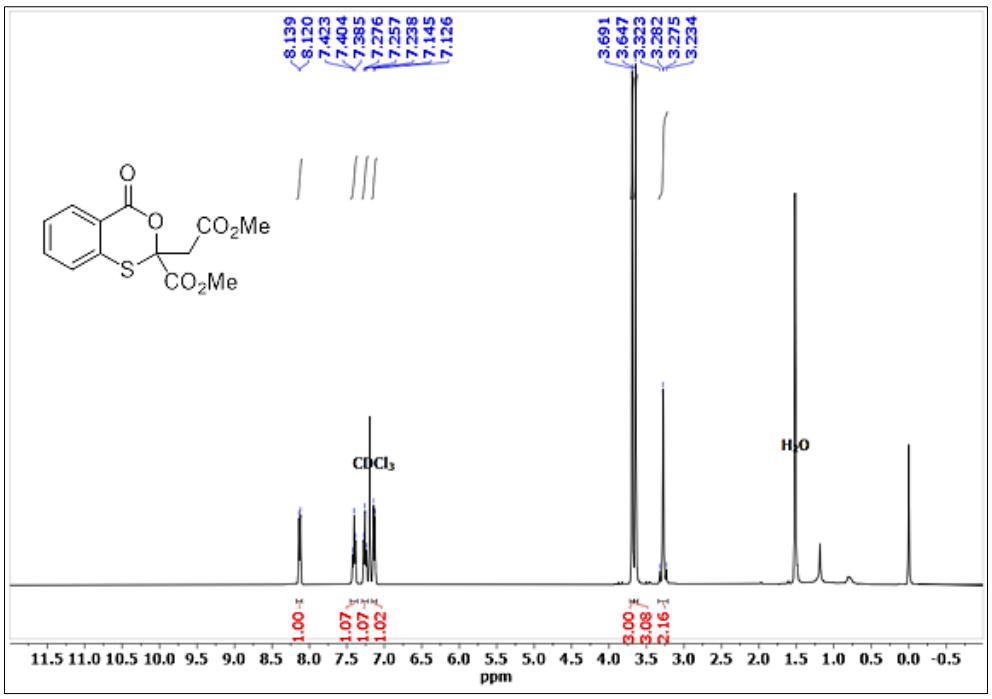


Figure 5.26 ^{1}H NMR spectrum of **5.3ea**

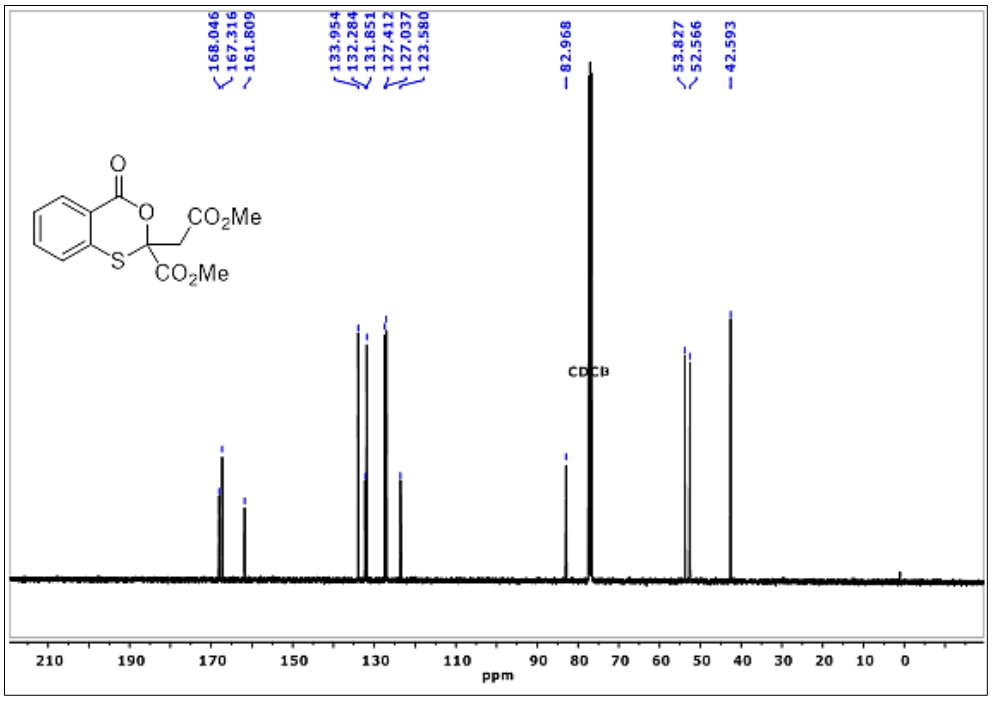


Figure 5.27 ^{13}C NMR spectrum of **5.3ea**

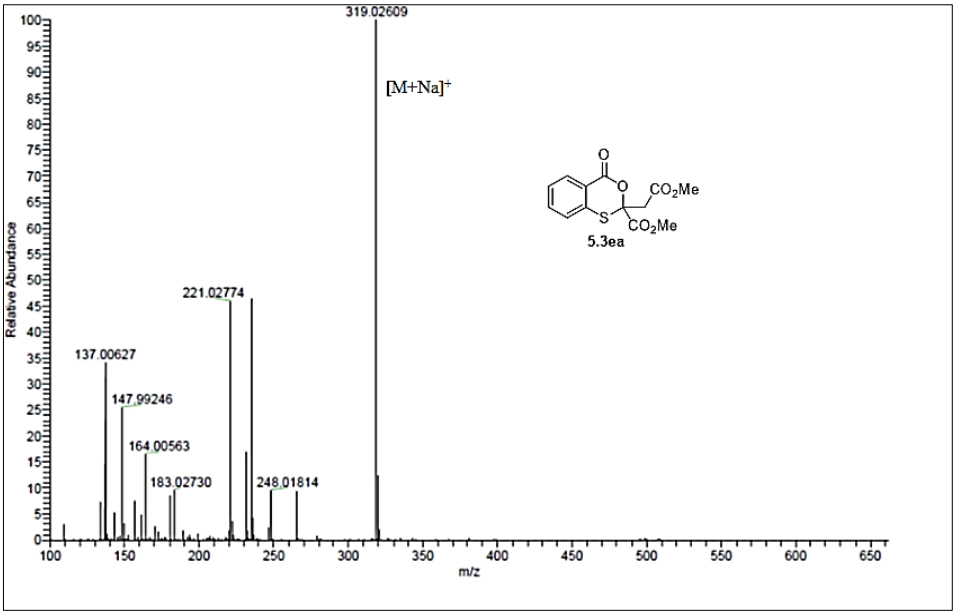


Figure 5.28 HRMS spectrum of **5.3ea**

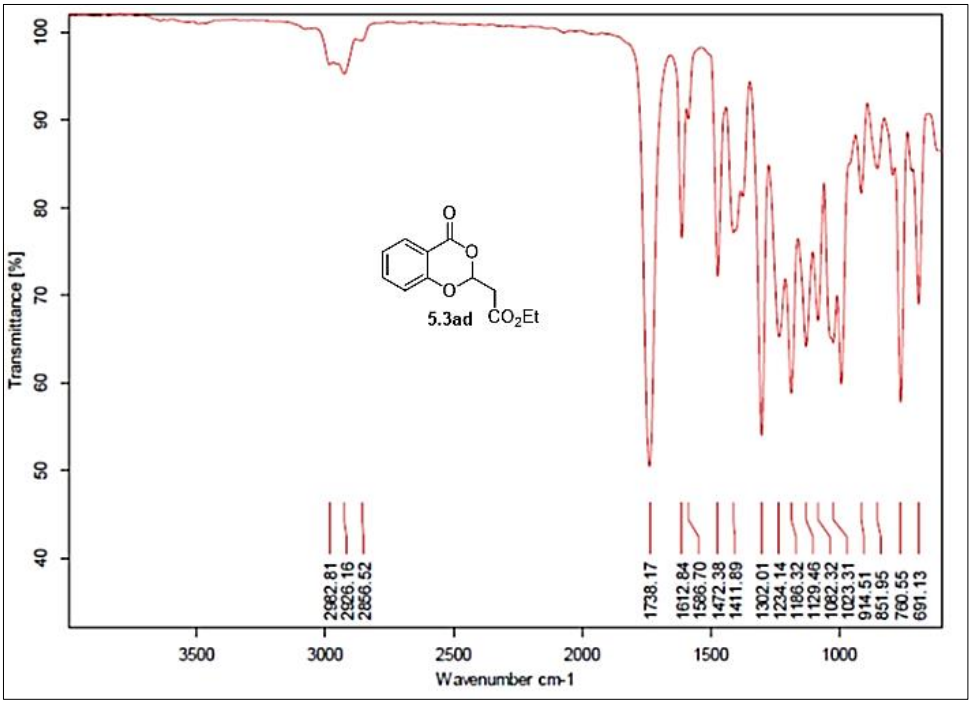


Figure 5.29 FTIR spectrum of **5.3ad**

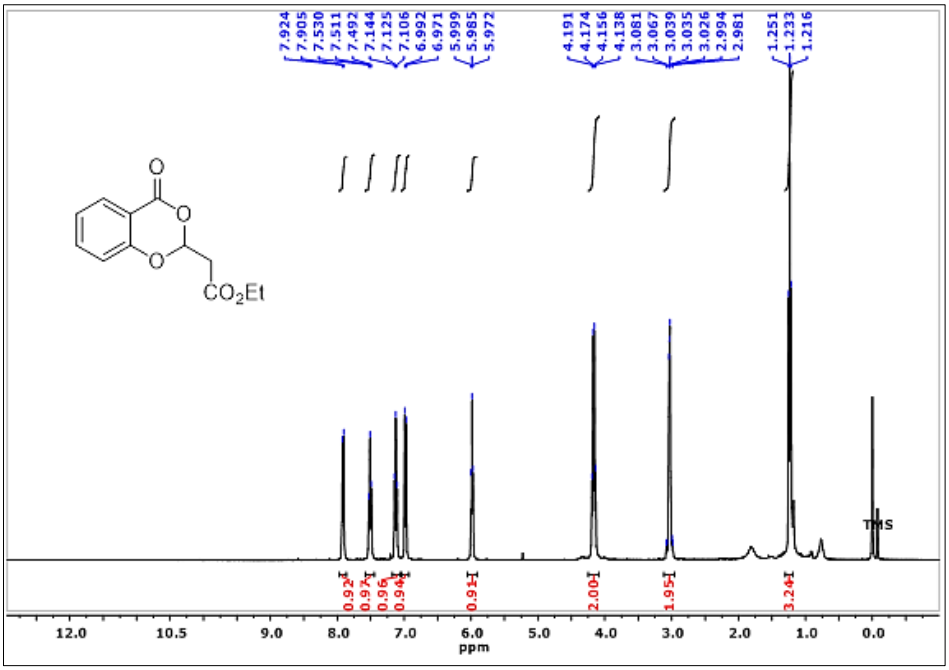


Figure 5.30 ^{1}H NMR spectrum of **5.3ad**

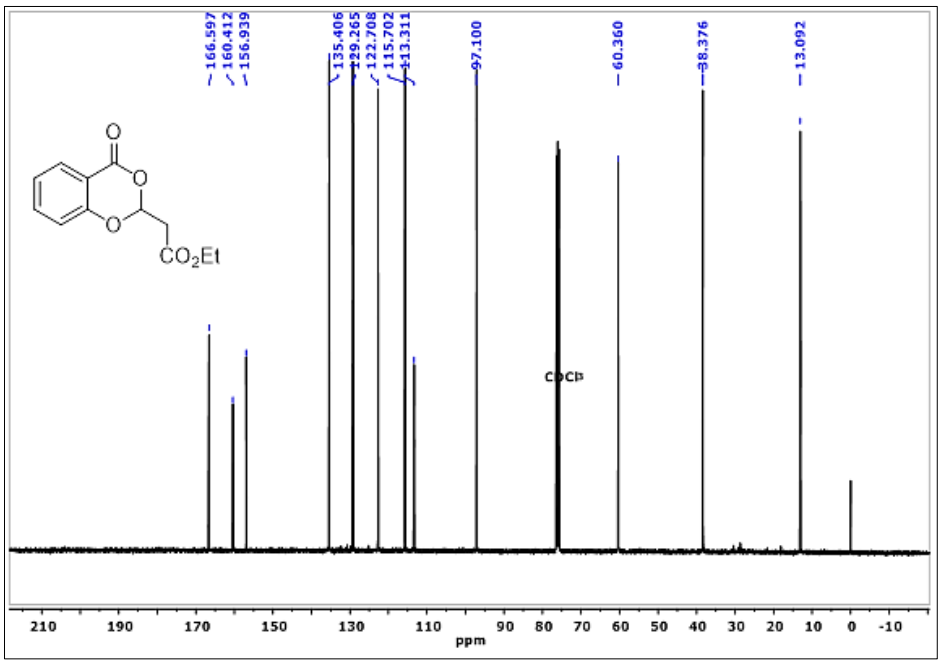


Figure 5.31 ^{13}C NMR spectrum of **5.3ad**

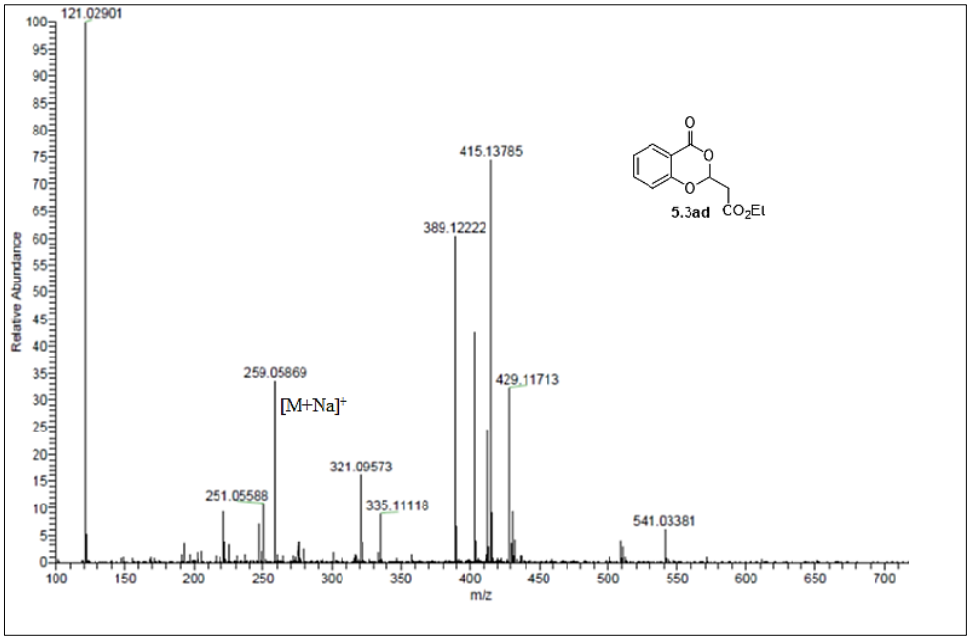


Figure 5.32 HRMS spectrum of **5.3ad**

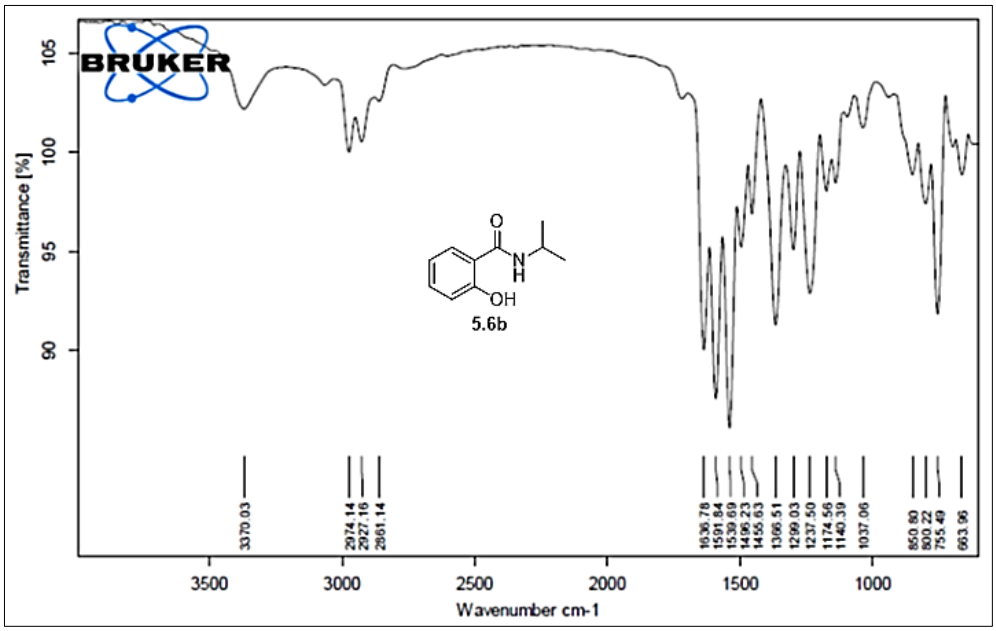


Figure 5.33 FTIR spectrum of **5.6b**

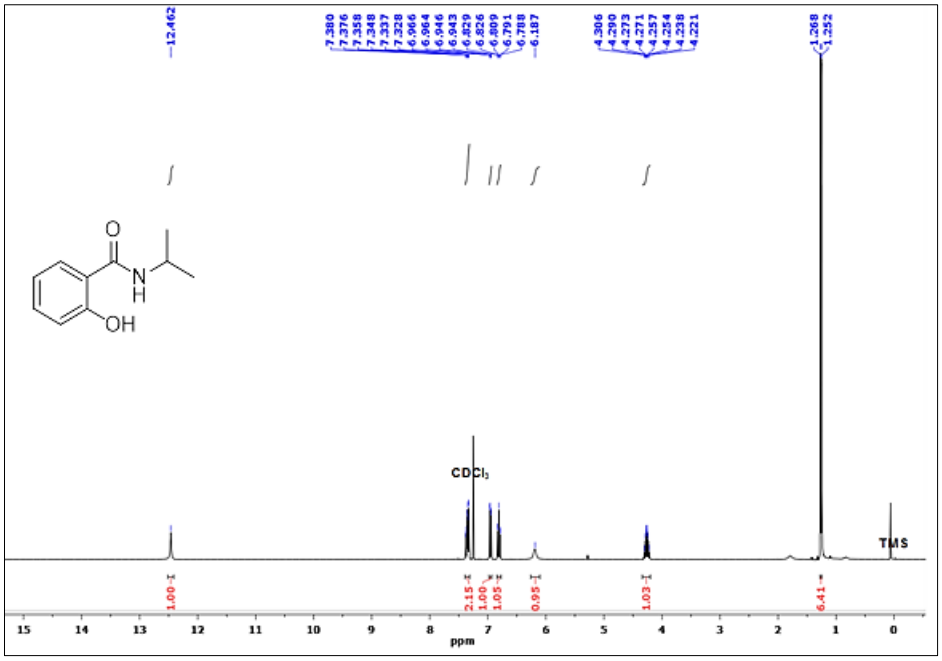


Figure 5.34 ^{1}H NMR spectrum of **5.6b**

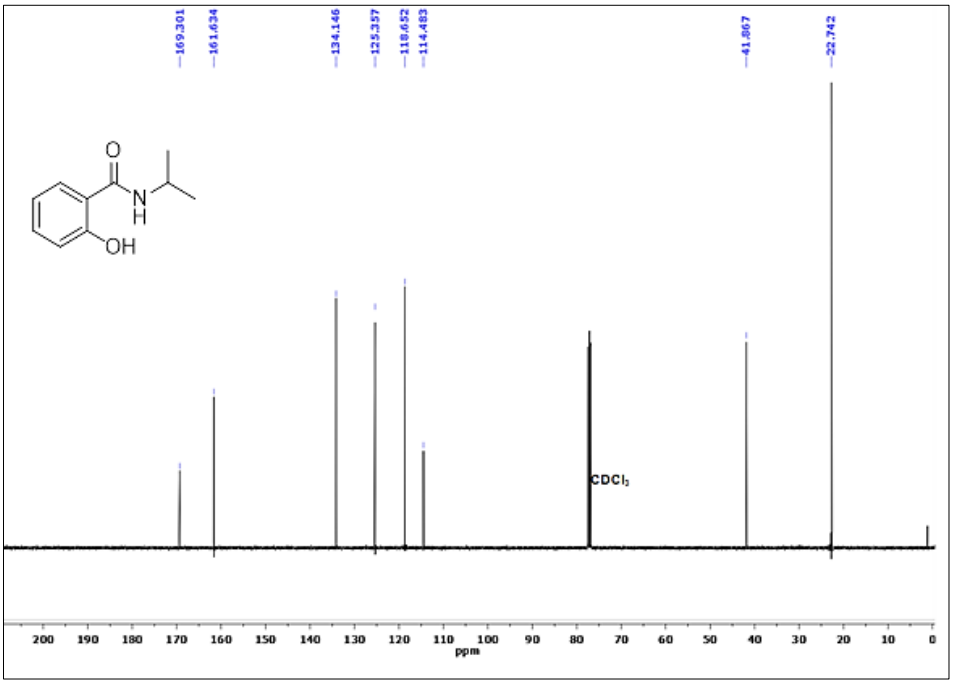


Figure 5.35 ^{13}C NMR spectrum of **5.6b**

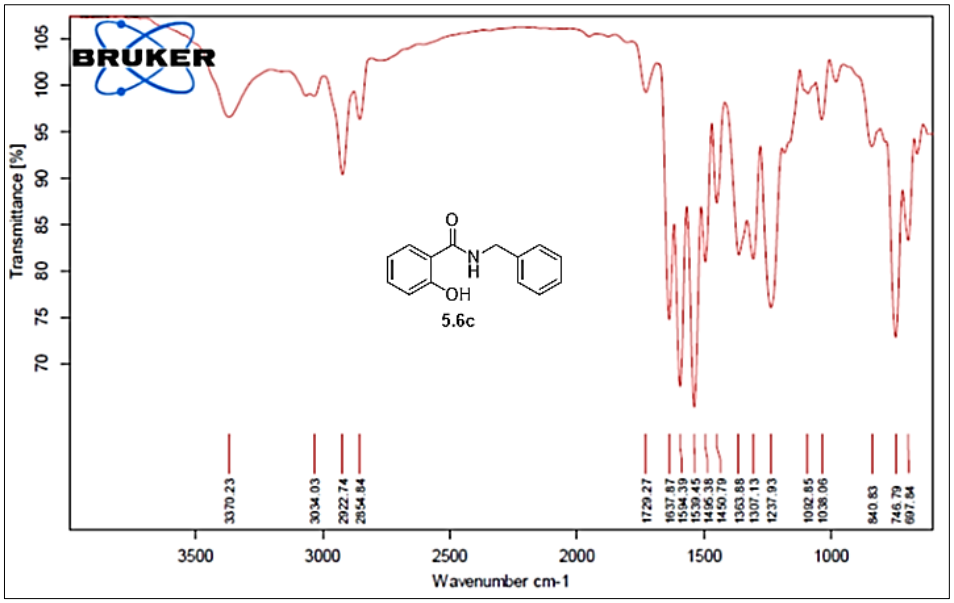


Figure 5.36 FTIR spectrum of **5.6c**

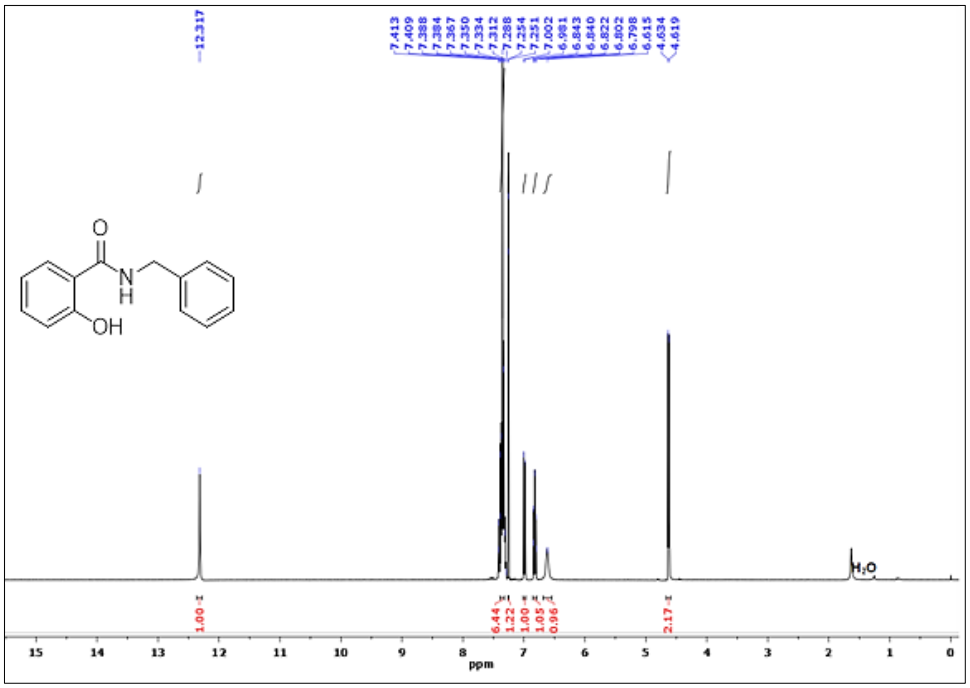


Figure 5.37 ^{1}H NMR spectrum of **5.6c**

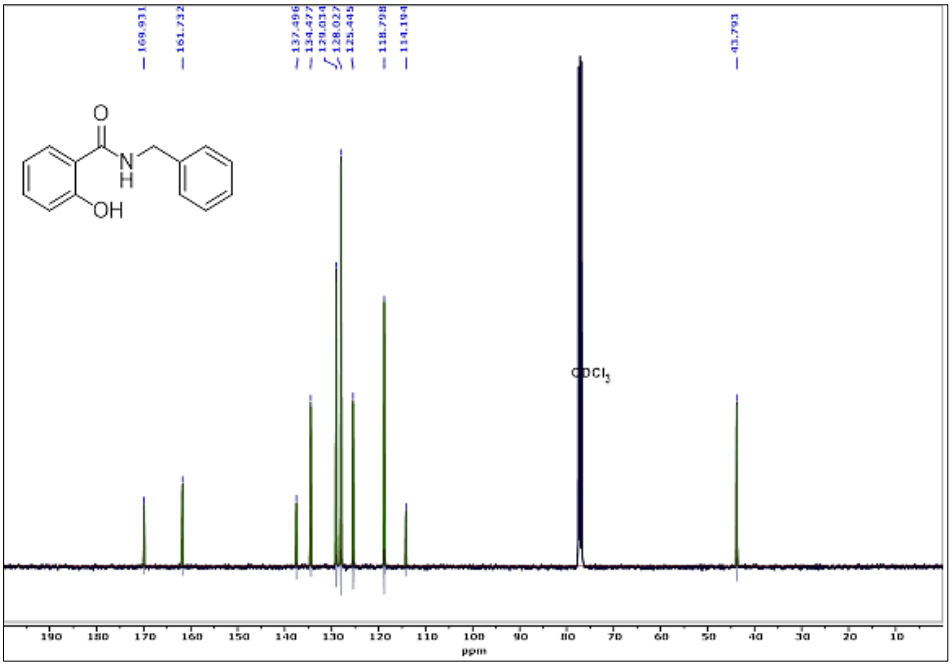


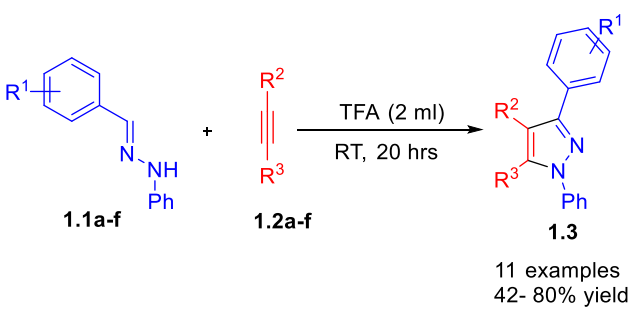
Figure 5.38 ^{13}C NMR spectrum of **5.6c**

CHAPTER 6

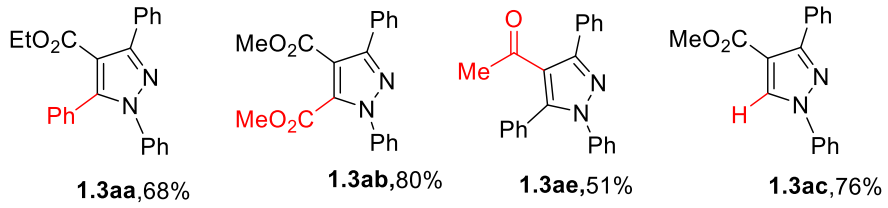
SUMMARY AND CONCLUSIONS

Development of facile synthetic methodologies for the construction of potential compounds are always a fascinating area in synthetic organic chemistry. The work entitled "Facile Synthetic Routes to Functionalized Nitrogen and Oxygen Heterocycles via Zwitterion Annulations" encompasses mild, robust and efficient one-pot synthetic protocols towards the synthesis of various nitrogen and oxygen heterocycles. Our idea was to propose modified strategies leading to the formation of valuable small and hybrid heterocycles from easily accessible substrates. The target compounds were synthesized via appropriate one-pot annulations. All the reactions were optimized to acquire maximum yield. Final compounds were purified either by column chromatography or by recrystallization using appropriate solvent mixtures.

Considering the biological significance of pyrazole, we started our initial investigations on the studies of the reactivity of hydrazone towards cyclic annulations to generate nitrogen heterocycles. A systematic survey on various reaction parameters led us to a metal –free, acid promoted synthetic pathway starting from readily accessible N-aryl hydrazones and acetylenic esters. Hydrazones have been used as an effective substrate for the development of many heterocycles including pyrazoles. Interestingly, hydrazones annulated across both symmetrical and unsymmetrical acetylenic esters, especially the terminal ones such as ethyl propiolate and methyl propiolate. Acetylenic ketones also reacted to afford pyrazole, whereas 3-phenylpropiolonitrile and the symmetrical diphenyl acetylene failed to yield the product. The substituted pyrazoles were obtained in good to moderate yields using hydrazones with electron withdrawing or electron donating groups on the phenyl ring of the aryl aldehyde. Wide range of functional group tolerance was observed for the proposed reaction methodology. Variously substituted pyrazoles with different electronic natures were isolated after column chromatography.

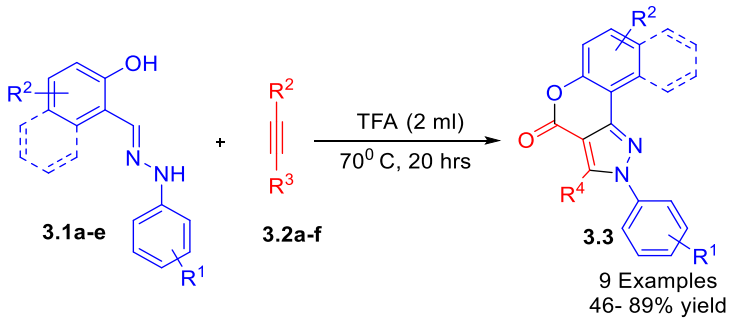


Scheme 6.1



Scheme 6.2 Pyrazole derivatives with diverse substitution pattern

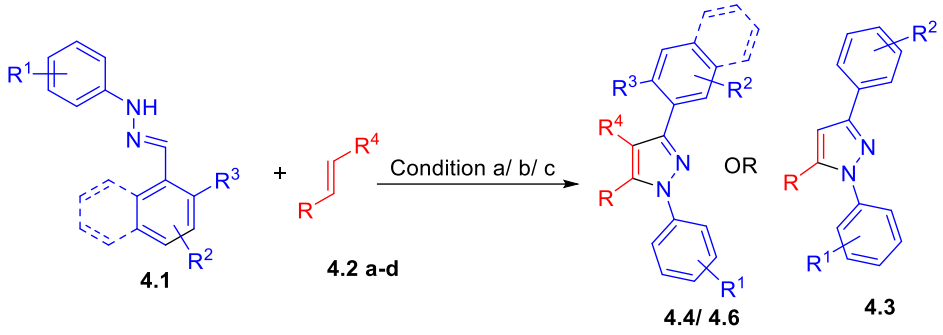
The strategy was further extended to the synthesis of chromenopyrazole derivatives, taking salicylaldehyde hydrazone derivatives instead of N-aryl hydrazones. The expected lactonization was completed at elevated temperature. Salicylaldehyde hydrazones and 2-hydroxyl naphthaldehyde hydrazones annulated across acetylenic esters with various substitution patterns. The one-pot generation of this hybrid polycycle was executed efficiently in a metal-free, step-economic manner.



Scheme 6.3

Further investigations to expand the scope of this annulation strategy was carried out on electron deficient olefins. Nitroolefins, alkyl acrylates, acrylonitrile, and other electron-deficient alkenes have been demonstrated to react with hydrazones to synthesize pyrazoles. The reaction between hydrazones and various alkenes was examined to expedite the 1, 3-dipolar cycloaddition reaction between activated alkenes and hydrazones. A detailed optimization study was conducted to derive the best condition for annulation reactions of each alkene. Olefins with different electron withdrawing groups selectively reacted with N-aryl hydrazones under specific conditions. Trans- β- nitrostyrene yielded pyrazole in 1, 2- DCE+ TFA (3:1) mixture, while α, β- unsaturated esters yielded the product in pure TFA. Surprisingly, the

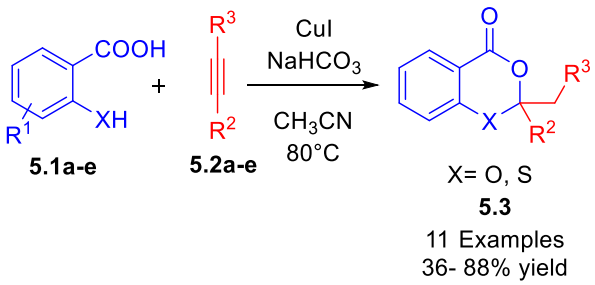
annulation of hydrazones across methyl vinyl ketones afforded the pyrazole in pure 1, 2- DCE at 80°C.



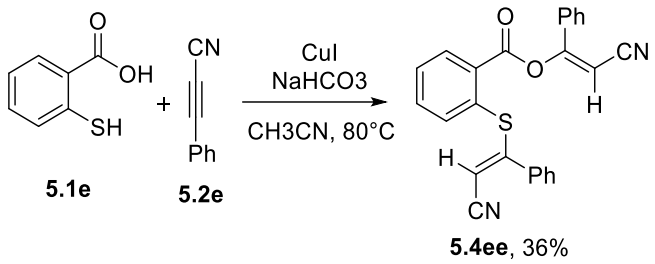
a) Hydrazone (1 equiv.), Alkene (1.2 equiv.), 1,2- DCE:TFA (3:1), rt/ 6-7h.
b) Hydrazone (1 equiv.), Alkene (1.5 equiv.), 1,2-DCE (2 ml), 80°C/ 48h
c) Hydrazone (1 equiv.), Alkene (1.2 equiv.), TFA (2 ml), rt/ 20 h.

Scheme 6.4

Due to our continued interest in the development of novel and modified synthetic routes to heterocycles, synthetically relevant benzodioxinones were prepared from commercially available salicylic acids and acetylenic esters. To the best of our knowledge, this is the first report on the synthesis of benzo[d][1,3] dioxin-4-ones from salicylic acid and acetylenic esters though the corresponding benzo-1,3-oxathiine route has already been documented. Interestingly, both disubstituted acetylenic esters – such as DMAD and diethyl acetylenedicarboxylate– and monosubstituted acetylenic esters – such as methyl propiolate and ethyl propiolate – were equally effective in the optimized conditions affording the benzo[d][1,3]dioxin-4-one derivatives in moderate to good yields. The reaction between thiosalicylic acid and 3-phenylpropiolonitrile yielded a 1:2 adduct 2-cyano-1-phenylvinyl(2-(2-cyano-1,2-diphenylvinyl)-thio)benzoate as the final product.

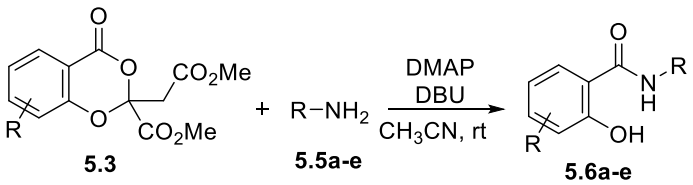


Scheme 6.5



Scheme 6.6

We treated the final 1, 3-benzodioxinones with various amines expecting easy access to salicylamides. We treated benzodioxinone derivatives and n-propylamine in presence of DMAP (10 mol%) and DBU (1 equiv.) in acetonitrile at room temperature for 8 h. The reaction was successful, and the expected salicylamide was formed in good yield. The strategy found successful with various primary amines though secondary amines and anilines were not effective.



Scheme 6.7

REFERENCES

Acheson, R. M., Hodgson, S. J., and Wright, R. G. M. (1976). "Addition reactions of heterocyclic compounds. Part LXV. Synthesis, tautomerism, and rearrangement of some 2H- and 4H-quinolizine esters." *J. Chem. Soc. Perkin Trans. 1*, (18), 1911–1915.

Adib, M., Sheibani, E., Mostofi, M., Ghanbary, K., and Bijanzadeh, H. R. (2006). "Efficient highly diastereoselective synthesis of 1,8a-dihydro-7H-imidazo[2,1-b][1,3]oxazines." *Tetrahedron*, 62(14), 3435–3438.

Aggarwal, V. K., Vicente, J. de, and Bonnert, R. V. (2003). "A Novel One-Pot Method for the Preparation of Pyrazoles by 1,3-Dipolar Cycloadditions of Diazo Compounds Generated in Situ." *J. Org. Chem.*, 68(13), 5381–5383.

Ahmad, T., and Ullah, N. (2021). "The oxa-Michael reaction in the synthesis of 5- and 6-membered oxygen-containing heterocycles." *Org. Chem. Front.*, 8(6), 1329–1344.

Arbačiauskiene, E., Kazlauskas, K., Miasojedovas, A., Juršenas, S., Jankauskas, V., Holzer, W., Getautis, V., and Šačkus, A. (2010). "Multifunctional polyconjugated molecules with carbazolyl and pyrazolyl moieties for optoelectronic applications." *Synth. Met.*, 160(5–6), 490–498.

Arora, P., Arora, V., Lamba, H. S., and Wadhwa, D. (2012). "IMPORTANCE OF HETEROCYCLIC CHEMISTRY: A REVIEW." *IJPSR*, 3(9), 2947–2954.

Bajwa, N., and Jennings, M. P. (2006). "Efficient and selective reduction protocols of the 2,2-dimethyl-1,3- benzodioxan-4-one functional group to readily provide both substituted salicylaldehydes and 2-hydroxybenzyl alcohols." *J. Org. Chem.*, 71(9), 3646–3649.

Bakthadoss, M., and Agarwal, V. (2018). "Synthesis of Highly Functionalized Tricyclic Chromenopyrazole Frameworks *via* Intramolecular Azomethine Imine 1,3-Dipolar Cycloaddition (IAIDC)." *ChemistrySelect*, 3(24), 6960–6964.

Balan, D., Burns, C. J., Fisk, N. G., Hügel, H., Huang, D. C. S., Segal, D., White, C., Wagler, J., and Rizzacasa, M. A. (2012). "Synthesis and biological evaluation of a

potent salicylihalamide A lactam analogue." *Org. Biomol. Chem.*, 10(40), 8147–8153.

Bhaskaran, R. P., Janardhanan, J. C., and Babu, B. P. (2020). "Metal-Free Synthesis of Pyrazoles and Chromenopyrazoles from Hydrazones and Acetylenic Esters." *ChemistrySelect*, 5(16), 4822–4825.

Brannock, K. C., Bell, A., Burpitt, R. D., and Kelly, C. A. (2002). "Enamine Chemistry. IV. Cycloaddition Reactions of Enamines Derived from Aldehydes and Acyclic Ketones1,2." *J. Org. Chem.*, 29(4), 801–812.

Burgart, Y. V., Shchur, I. V., Shchegolkov, E. V., and Saloutin, V. I. (2020). "Synthesis and biological activity of polyfluorinated p-aminosalicylic acids and their amides." *Mendeleev Commun.*, 30(5), 636–638.

Chang, S. Y., Chen, J. L., Chi, Y., Cheng, Y. M., Lee, G. H., Jiang, C. M., and Chou, P. T. (2007). "Blue-emitting platinum(II) complexes bearing both pyridylpyrazolate chelate and bridging pyrazolate ligands: Synthesis, structures, and photophysical properties." *Inorg. Chem.*, 46(26), 11202–11212.

Chen, X., Wang, H., Doitomi, K., Ooi, C. Y., Zheng, P., Liu, W., Guo, H., Yang, S., Song, B. A., Hirao, H., and Chi, Y. R. (2017). "A reaction mode of carbene-catalysed aryl aldehyde activation and induced phenol OH functionalization." *Nat. Commun. 2017 81*, 8(1), 1–8.

Chen, Y., Fuyue, L., Wang, G., Wang, H., Lu, C., Guo, H., Amant, C. St., Sun, S., and Xing, Y. (2019). "Synthesis of 1,2,4-oxadiazolidines via [3+2] cycloaddition of nitrones with carbodiimides." *New J. Chem.*, 43(11), 4329–4332.

Chen, Z., Zheng, Y., and Ma, J. A. (2017). "Use of a Traceless Activating and Directing Group for the Construction of Trifluoromethylpyrazoles: One-Pot Transformation of Nitroolefins and Trifluorodiazoethane." *Angew. Chemie - Int. Ed.*, 56(16), 4569–4574.

Chianelli, D., Rucker, P. V., Roland, J., Tully, D. C., Nelson, J., Liu, X., Bursulaya, B., Hernandez, E. D., Wu, J., Prashad, M., Schlama, T., Liu, Y., Chu, A., Schmeits, J., Huang, D. J., Hill, R., Bao, D., Zoll, J., Kim, Y., Groessl, T., McNamara, P., Liu, B., Richmond, W., Sancho-Martinez, I., Phimister, A., Seidel, H. M., Badman, M. K.,

Joseph, S. B., Laffitte, B., and Molteni, V. (2020). “Nidufexor (LMB763), a Novel FXR Modulator for the Treatment of Nonalcoholic Steatohepatitis.” *J. Med. Chem.*, 63(8), 3868–3880.

Combrink, K. D., Gulgeze, H. B., Yu, K. L., Pearce, B. C., Trehan, A. K., Wei, J., Deshpande, M., Krystal, M., Torri, A., Luo, G., Cianci, C., Danetz, S., Tiley, L., and Meanwell, N. A. (2000). “Salicylamide inhibitors of influenza virus fusion.” *Bioorganic Med. Chem. Lett.*, 10(15), 1649–1652.

Corre, L. Le, Tak-Tak, L., Guillard, A., Prestat, G., Gravier-Pelletier, C., and Busca, P. (2014). “Microwave-assisted preparation of 4-amino-3-cyano-5-methoxycarbonyl-N-arylpyrazoles as building blocks for the diversity-oriented synthesis of pyrazole-based polycyclic scaffolds.” *Org. Biomol. Chem.*, 13(2), 409–423.

Csókás, D., Ho, A. X. Y., Ramabhadran, R. O., and Bates, R. W. (2019). “How an early or late transition state impacts the stereoselectivity of tetrahydropyran formation by intramolecular oxa-Michael addition.” *Org. Biomol. Chem.*, 17(25), 6293–6304.

Dai, T., Li, Q., Zhang, X., and Yang, C. (2019). “Substituent-Oriented Synthesis of Substituted Pyrazoles/Chromeno[3,2-c]pyrazoles via Sequential Reactions of Chromones/3-Chlorochromones and Tosylhydrazones.” *J. Org. Chem.*, 84(9), 5913–5921.

Das, P., Gondo, S., Tokunaga, E., Sumii, Y., and Shibata, N. (2018). “Anionic Triflyldiazomethane: Generation and Its Application for Synthesis of Pyrazole-3-triflones via [3 + 2] Cycloaddition Reaction.” *Org. Lett.*, 20(3), 558–561.

Dayakar, C., Kumar, B. S., Sneha, G., Sagarika, G., Meghana, K., Ramakrishna, S., Prakasham, R. S., and China Raju, B. (2017). “Synthesis, pharmacological activities and molecular docking studies of pyrazolyltriazoles as anti-bacterial and anti-inflammatory agents.” *Bioorganic Med. Chem.*, 25(20), 5678–5691.

De, K., Bhanja, P., Bhaumik, A., and Mukhopadhyay, C. (2017). “An ExpeditiousSynthesis of Spiro[chromeno[2,3-c]pyrazole-4,3′-indolin]-2′5-diones Catalysed by RecyclableSpinel $ZnFe_2O_4$ Nanopowder.” *ChemistrySelect*, 2(17), 4857–

4865.

Deng, X., Liang, J. T., and Mani, N. S. (2014). “Regioselective Synthesis of 4-Nitro- or 4-Chloro-Tetrasubstituted Pyrazoles from Hydrazones and β-Halo-β-nitrostyrenes.” *Eur. J. Org. Chem.*, 2014(2), 410–417.

Deng, X., and Mani, N. S. (2006). “Reaction of N-monosubstituted hydrazones with nitroolefins: A novel regioselective pyrazole synthesis.” *Org. Lett.*, 8(16), 3505–3508.

Deng, X., and Mani, N. S. (2008). “Regioselective Synthesis of 1,3,5-Tri- and 1,3,4,5-Tetrasubstituted Pyrazoles from *N* -Arylhydrazones and Nitroolefins.” *J. Org. Chem.*, 73(6), 2412–2415.

Deng, X., and Mani, N. S. (2008). “Base-mediated reaction of hydrazones and nitroolefins with a reversed regioselectivity: A novel synthesis of 1,3,4-Trisubstituted pyrazoles.” *Org. Lett.*, 10(6), 1307–1310.

Desai, V. G., Satardekar, P. C., Polo, S., and Dhumaskar, K. (2011). “Regioselective Synthesis of 1,3,5-Trisubstituted Pyrazoles.” *Synth. Commun.*, 42(6), 836–842.

Dhanju, S., Caravana, A. C., and Thomson, R. J. (2020). “Access to α-Pyrazole and α-Triazole Derivatives of Ketones from Oxidative Heteroarylation of Silyl Enolethers.” *Org. Lett.*, 22(20), 8055–8058.

Divya, K. V. L., Meena, A., and Suja, T. D. (2016). “Unified Approach to Pyrazole-Fused Heterocyclic and Carbocyclic Motifs through One-Pot Condensation and Intramolecular Dipolar Cycloaddition Reaction.” *Synthesis.*, 48(23), 4207–4212.

Ding, H., Ma, C., Yang, Y., and Wang, Y. (2005). “Unexpected reaction of dimethyl acetylenedicarboxylate with in situ generated arylketenes catalyzed by 1-methylimidazole.” *Org. Lett.*, 7(11), 2125–2127.

Elliott, D. C., Ma, T. K., Selmani, A., Cookson, R., Parsons, P. J., and Barrett, A. G. M. (2016). “Sequential Ketene Generation from Dioxane-4,6-dione-keto-dioxinones for the Synthesis of Terpenoid Resorcylates.” *Org. Lett.*, 18(8), 1800–1803.

Enders, D., Wang, C., and Liebich, J. X. (2009). “Organocatalytic Asymmetric Aza-

Michael Additions." *Chem. Eur. J.*, 15(42), 11058–11076.

Erguven, H., Zhou, C., and Arndtsen, B. A. (2021). "Multicomponent formation route to a new class of oxygen-based 1,3-dipoles and the modular synthesis of furans." *Chem. Sci.*, 12(45), 15077–15083.

Evans, P. A., Huang, M. H., Lawler, M. J., and Maroto, S. (2012). "Total synthesis of marinomycin A using salicylate as a molecular switch to mediate dimerization." *Nat. Chem.*, 4(8), 680–684.

F. Nising, C., and Stefan Bräse. (2008). "The oxa-Michael reaction: from recent developments to applications in natural product synthesis." *Chem. Soc. Rev.*, 37(6), 1218–1228.

Fan, M. J., Li, G. Q., and Liang, Y. M. (2006). "DABCO catalyzed reaction of various nucleophiles with activated alkynes leading to the formation of alkenoic acid esters, 1,4-dioxane, morpholine, and piperazinone derivatives." *Tetrahedron*, 62(29), 6782–6791.

Fan, Z., Feng, J., Hou, Y., Rao, M., and Cheng, J. (2020). "Copper-Catalyzed Aerobic Cyclization of β,γ-Unsaturated Hydrazones with Concomitant C═C Bond Cleavage." *Org. Lett.*, 22(20), 7981–7985.

Fricero, P., Bialy, L., Brown, A. W., Czechtizky, W., Méndez, M., and Harrity, J. P. A. (2017). "Synthesis and Modular Reactivity of Pyrazole 5-Trifluoroborates: Intermediates for the Preparation of Fully Functionalized Pyrazoles." *J. Org. Chem.*, 82(3), 1688–1696.

Fustero, S., Román, R., Sanz-Cervera, J. F., Simón-Fuentes, A., Cuñat, A. C., Villanova, S., and Murguía, M. (2008). "Improved Regioselectivity in Pyrazole Formation through the Use of Fluorinated Alcohols as Solvents: Synthesis and Biological Activity of Fluorinated Tebufenpyrad Analogs." *J. Org. Chem.*, 73(9), 3523–3529.

Fustero, S., Simón-Fuentes, A., and Sanz-Cervera, J. F. (2009). "Recent Advances in the Synthesis of Pyrazoles. A Review." *Org. Prep. Proced. Int.*, 41(4), 253–290.

Ganesan, J. S., Sepperumal, M., Balasubramaniem, A., and Ayyanar, S. (2020). "A novel pyrazole bearing imidazole frame as ratiometric fluorescent chemosensor for Al^{3+}/Fe^{3+} ions and its application in HeLa cell imaging." *Spectrochim. Acta Part A Mol. Biomol. Spectrosc.*, 230, 117993.

Geisler, L. K., Nguyen, S., and Forsyth, C. J. (2004). "Synthesis of the azaspiracid-1 trioxadispiroketal." *Org. Lett.*, 6(23), 4159–4162.

Ghosez, L., and Perez, C. de. (1971). "Cycloadditions of Keteneimines of Ynamines." *Angew. Chem. Int. Ed.*, 10(3), 184–185.

Glukhacheva, V. S., Il'yasov, S. G., Kazantsev, I. V., Shestakova, E. O., Il'yasov, D. S., Eltsov, I. V., Nefedov, A. A., and Gatilov, Y. V. (2021). "New Reaction Products of Acetylacetone with Semicarbazide Derivatives." *ACS Omega*, 6(12), 8637–8645.

Godumala, M., Choi, S., Park, S. Y., Cho, M. J., Kim, H. J., Ahn, D. H., Moon, J. S., Kwon, J. H., and Choi, D. H. (2018). "Chromenopyrazole-Based Bipolar Blue Host Materials for Highly Efficient Thermally Activated Delayed Fluorescence Organic Light-Emitting Diodes." *Chem. Mater.*, 30(15), 5005–5012.

Godumala, M., Yoon, J., Lee, C., Jeong, J. E., Park, S., Woo, H. Y., Cho, M. J., and Choi, D. H. (2019). "Chromenopyrazole-based bipolar host materials for solution-processable thermally activated delayed fluorescence OLEDs exhibiting high efficiency and low roll-off." *Chem. Commun.*, 55(86), 12952–12955.

Golovanov, A. A., Odin, I. S., Gusev, D. M., Vologzhanina, A. V., Sosnin, I. M., and Grabovskiy, S. A. (2021). "Reactivity of Cross-Conjugated Enynones in Cyclocondensations with Hydrazines: Synthesis of Pyrazoles and Pyrazolines." *J. Org. Chem.*, 86(10), 7229–7241.

Götzinger, A. C., Theßeling, F. A., Hoppe, C., and Müller, T. J. J. (2016). "One-Pot Coupling–Coupling–Cyclocondensation Synthesis of Fluorescent Pyrazoles." *J. Org. Chem.*, 81(21), 10328–10338.

Gracia Retamosa, M. de, Matador, E., Monge, D., Lassaletta, J. M., and Fernández, R. (2016). "Hydrazones as Singular Reagents in Asymmetric Organocatalysis." *Chem.*

Eur. J., 22(38), 13430–13445.

Grover, J., Kumar, V., Sobhia, M. E., and Jachak, S. M. (2014). "Synthesis, biological evaluation and docking analysis of 3-methyl-1-phenylchromeno[4,3-c]pyrazol-4(1H)-ones as potential cyclooxygenase-2 (COX-2) inhibitors." *Bioorg. Med. Chem. Lett.*, 24(19), 4638–4642.

Guo, Y., Wang, G., Wei, L., and Wan, J.P. (2019). "Domino C-H Sulfonylation and Pyrazole Annulation for Fully Substituted Pyrazole Synthesis in Water Using Hydrophilic Enaminones." *J. Org. Chem.*, 84(5), 2984–2990.

Hariprasad, K. S., Anand, A., Rathod, B. B., Zehra, A., Tiwari, A. K., Prakasham, R. S., and Raju, B. C. (2017). "Neoteric Synthesis and Biological Activities of Chromenopyrazolones, Tosylchromenopyrazolones, Benzoylcoumarins." *ChemistrySelect*, 2(32), 10628–10634.

Hariprasad, K. S., Prasad, K. V., and Raju, B. C. (2016). "$La(OTf)_3$ catalyzed reaction of salicylaldehyde phenylhydrazones with β-ketoesters and activated alkynes: facile approach for the preparation of chromenopyrazolones." *RSC Adv.*, 6(110), 108654–108661.

Hassan, A. S., Moustafa, G. O., Awad, H. M., Nossier, E. S., and Mady, M. F. (2021). "Design, synthesis, anticancer evaluation, enzymatic assays, and a molecular modeling study of novel pyrazole-indole hybrids." *ACS Omega*, 6(18), 12361–12374.

He, X., Li, Y., Wang, M., Chen, H.-X., Chen, B., Liang, H., Zhang, Y., Pang, J., and Qiu, L. (2018). "Highly efficient synthesis of benzodioxins with a 2-site quaternary carbon structure by secondary amine-catalyzed dual Michael cascade reactions." *Org. Biomol. Chem.*, 16(30), 5533–5538.

Heller, S. T., and Natarajan, S. R. (2006). "1,3-Diketones from Acid Chlorides and Ketones: A Rapid and General One-Pot Synthesis of Pyrazoles." *Org. Lett.*, 8(13), 2675–2678.

Hoffmann, R., and Woodward, R. B. (2002). "Selection Rules for Concerted Cycloaddition Reactions." *J. Am. Chem. Soc.*, 87(9), 2046–2048.

Hong, B. C., Kotame, P., Tsal, C. W., and Liao, J. H. (2010). “Enantioselective total synthesis of (+)-conicol via cascade three-component organocatalysis.” *Org. Lett.*, 12(4), 776–779.

Houk, K. N., GonzAlez, J., and Li, Y. (1995). “Pericyclic Reaction Transition States: Passions and Punctilios, 1935-1995.” *Acc. Chem. Res.*, 28(2), 81–90.

Huisgen, R. (1963). “1,3-Dipolar Cycloadditions. Past and Future.” *Angew. Chemie Int. Ed.*, 2(10), 565–598.

Huisgen, R. (1968). “Cycloadditions - Definition, Classification, and Characterization.” *Angew. Chem. Int. Ed.*,7(5), 321–328.

Huisgen, R. (2002). “1,3-Dipolar cycloadditions. 76. Concerted nature of 1,3-dipolar cycloadditions and the question of diradical intermediates.” *J. Org. Chem.*, 41(3), 403–419.

Huisgen, R., and Herbig, K. (1965). “1.4-Dipolare Cycloadditionen, I. Reaktionen der Azomethine mit Acetylendicarbonsäureester.” *Justus Liebigs Ann. Chem.*, 688(1), 98–112.

Huisgen, R., Szeimies, G., and Möbius, L. (1967). “1.3-Dipolare Cycloadditionen, XXXII. Kinetik der Additionen organischer Azide an CC-Mehrfachbindungen.” *Chem. Ber.*, 100(8), 2494–2507.

Jackson, P. A., Widen, J. C., Harki, D. A., and Brummond, K. M. (2016). “Covalent Modifiers: A Chemical Perspective on the Reactivity of α,β-Unsaturated Carbonyls with Thiols via Hetero-Michael Addition Reactions.” *J. Med. Chem.*, 60(3), 839–885.

Jun Zhu, Brandon M. Lines, Michael D. Ganton, Michael A. Kerr, and, and Workentin, M. S. (2008). “Efficient Synthesis of Isoxazolidine-Tethered Monolayer-Protected Gold Nanoparticles (MPGNs) via 1,3-Dipolar Cycloadditions under High-Pressure Conditions.” *J. Org. Chem.*, 73(3), 1099–1105.

Kamal, A., Sastry, K. N. V., Chandrasekhar, D., Mani, G. S., Adiyala, P. R., Nanubolu,

J. B., Singarapu, K. K., and Maurya, R. A. (2015). “One-Pot, Three-Component Approach to the Synthesis of 3,4,5-Trisubstituted Pyrazoles.” *J. Org. Chem.*, 80(9), 4325–4335.

Kandel, S., Sathish, V., Mathivathanan, L., Morozov, A. N., Mebel, A. M., and Raptis, R. G. (2019). “Aggregation induced emission enhancement (AIEE) of tripodal pyrazole derivatives for sensing of nitroaromatics and vapor phase detection of picric acid.” *New J. Chem.*, 43(19), 7251–7258.

Kasapidou, P. M., Zarganes-Tzitzikas, T., Tsoleridis, C. A., Stephanidou-Stephanatou, J., and Neochoritis, C. G. (2017). “Manipulating a Multicomponent Reaction: A Straightforward Approach to Chromenopyrazole Hybrid Scaffolds.” *Synthesis.*, 49(16), 3619–3632.

Katla, R., Chowrasia, R., Manjari, P. S., Silva, C. D. G. da, Santos, B. F. dos, and Domingues, N. L. C. (2016). “$[Ce(L\text{-}Pro)_2]_2$ (Oxa) as a heterogeneous recyclable catalyst: synthesis of pyrazoles under mild reaction conditions.” *New J. Chem.*, 40(11), 9471–9476.

Kawai, H., Yuan, Z., Tokunaga, E., and Shibata, N. (2012). “Regioselective synthesis of pyrazole triflones based on triflyl alkyne cycloadditions.” *Org. Lett.*, 14(20), 5330–5333.

Ke, X., Meng, L., Wan, X., Sun, Y., Guo, Z., Wu, S., Zhang, H., Li, C., and Chen, Y. (2020). “An oxygen heterocycle-fused fluorene based non-fullerene acceptor for high efficiency organic solar cells.” *Mater. Chem. Front.*, 4(12), 3594–3601.

Khan, H. P. A., and Chakraborty, T. K. (2018). “Diversity-oriented approach to N-Heterocyclic Compounds from α-Phenyl-β-enamino ester via a mitsunobu-michael reaction sequence.” *J. Org. Chem.*, 83(4), 2027–2039.

Kirkham, J. D., Edeson, S. J., Stokes, S., and Harrity, J. P. A. (2012). “Synthesis of Ynone Trifluoroborates toward Functionalized Pyrazoles.” *Org. Lett.*, 14(20), 5354–5357.

Knölker, H. J., and Boese, R. (1988). “A novel synthesis of the imidazo[1,2-a]pyridine

ring system.” *J. Chem. Soc. Chem. Commun.*, (17), 1151–1153.

Kong, Y., Tang, M., and Wang, Y. (2014). “Regioselective synthesis of 1,3,5-Trisubstituted Pyrazoles from N-Alkylated Tosylhydrazones and terminal Alkynes.” *Org. Lett.*, 16(2), 576–579.

Krasiński, A., Radić, Z., Manetsch, R., Raushel, J., Taylor, P., Sharpless, K. B., and Kolb, H. C. (2005). “In situ selection of lead compounds by click chemistry: Target-guided optimization of acetylcholinesterase inhibitors.” *J. Am. Chem. Soc.*, 127(18), 6686–6692.

Kulbitski, K., Nisnevich, G., and Gandelman, M. (2011). “Metal-Free Efficient, General and Facile Iododecarboxylation Method with Biodegradable Co-Products.” *Adv. Synth. Catal.*, 353(9), 1438–1442.

Kumar, R., Nair, D., and Namboothiri, I. N. N. (2014). “Reactions of vinyl sulfone with α-diazo-β-ketosulfone and Bestmann–Ohira reagent for the regioselective synthesis of highly functionalized pyrazoles.” *Tetrahedron*, 70(9), 1794–1799.

Kumar, R., and Namboothiri, I. N. N. (2011). “Regioselective Synthesis of Sulfonylpyrazoles via Base Mediated Reaction of Diazosulfones with Nitroalkenes and a Facile Entry into Withasomnine.” *Org. Lett.*, 13(15), 4016–4019.

Kurma, S. H., Sridhar, B., and Bhimapaka, C. R. (2021). “Direct Access for the Regio- And Stereoselective Synthesis of N-Alkenylpyrazoles and Chromenopyrazoles.” *J. Org. Chem.*, 86(3), 2271–2282.

Lagoja, I. M., and Clercq, E. De. (2008). “Anti-influenza virus agents: Synthesis and mode of action.” *Med. Res. Rev.*, 28(1), 1- 38.

Lanke, S. K., and Sekar, N. (2016). “Pyrazole based NLOphores: Synthesis, photophysical, DFT, TDDFT studies.” *Dye. Pigment.*, 127, 116–127.

Lee, Y.-G., Koyama, Y., Yonekawa, M., and Takata, T. (2009). “New Click Chemistry: Polymerization Based on 1,3-Dipolar Cycloaddition of a Homo Ditopic Nitrile N-Oxide and Transformation of the Resulting Polymers into Reactive Polymers.” *Macromolecules*, 42(20), 7709–7717.

Li, H., Liu, C., Zhang, Y., Sun, Y., Wang, B., and Liu, W. (2015). “Green Method for the Synthesis of Chromeno[2,3-c]pyrazol-4(1H)-ones through Ionic Liquid Promoted Directed Annulation of 5-(Aryloxy)-1H-pyrazole-4-carbaldehydes in Aqueous Media.” *Org. Lett.*, 17(4), 932–935.

Li, M., Pan, L., and Wen, L.-R. (2011). “Efficient Synthesis of [1,3]Oxazino[3,2-f]phenanthridine Derivatives by a Novel 1,4-Dipolar Cycloaddition Involving a Phenanthridine–Dimethyl Acetylenedicarboxylate Zwitterion and Aromatic Aldehydes.” *Helv. Chim. Acta*, 94(1), 169–177.

Liang, H., He, X., Zhang, Y., Chen, B., Ouyang, J. S., Li, Y., Pan, B., Subba Reddy, C. V., Chan, W. T. K., and Qiu, L. (2020). “Copper-catalyzed (4+1) and (3+2) cyclizations of iodonium ylides with alkynes.” *Chem. Commun.*, 56(77), 11429–11432.

Lin, F., Song, Q., Gao, Y., and Cui, X. (2014). “A catalyst-free, facile and efficient approach to cyclic esters: Synthesis of 4H-benzo[d][1,3]dioxin-4-ones.” *RSC Adv.*, 4(38), 19856–19860.

Liu, Y., Huang, M., and Wei, L. (2017). “Copper-catalyzed synthesis of benzo[d][1,3]dioxin-4-ones via tandem Ar–halogen bond hydroxylation and dichloromethane-based double Williamson etherification.” *New J. Chem.*, 41(12), 4776–4778.

v, Y., Meng, J., Li, C., Wang, X., Ye, Y., and Sun, K. (2021). “Update on the Synthesis of N-Heterocycles via Cyclization of Hydrazones (2017–2021).” *Adv. Synth. Catal.*, 363(23), 5235–5265.

Mani, K. S., Rajamanikandan, R., Ravikumar, G., Pandiyan, B. V., Kolandaivel, P., Ilanchelian, M., and Rajendran, S. P. (2018). “Highly Sensitive Coumarin–Pyrazolone Probe for the Detection of Cr^{3+} and the Application in Living Cells.” *ACS Omega*, 3(12), 17212–17219.

Marie Kissane, and R. Maguire, A. (2010). “Asymmetric 1,3-dipolar cycloadditions of acrylamides.” *Chem. Soc. Rev.*, 39(2), 845–883.

Martina, K., Tagliapietra, S., Veselov, V. V., and Cravotto, G. (2019). “Green Protocols

in Heterocycle Syntheses via 1,3-Dipolar Cycloadditions." *Front. Chem.*, 7(FEB), 95.

Matsuzaki, H., Takeda, N., Yasui, M., Ito, Y., Konishi, K., and Ueda, M. (2020). "Synthesis of Pyrazoles Utilizing the Ambiphilic Reactivity of Hydrazones." *Org. Lett.*, 22(23), 9249–9252.

Maurya, H. K., Kumar, C. P., Chandrasekharam, M., and Gupta, A. (2017). "Photophysical and electrochemical studies of highly fluorescent pyrazole and imidazole containing heterocycles." *Dye. Pigment.*, 136, 686–696.

Medina, F. G., Marrero, J. G., Macías-Alonso, M., González, M. C., Córdova-Guerrero, I., Teissier García, A. G., and Osegueda-Robles, S. (2015). "Coumarin heterocyclic derivatives: chemical synthesis and biological activity." *Nat. Prod. Rep.*, 32(10), 1472–1507.

Meunier, B. (2007). "Hybrid Molecules with a Dual Mode of Action: Dream or Reality?." *Acc. Chem. Res.*, 41(1), 69–77.

Mikhailov, K. I., Galenko, E. E., Galenko, A. V., Novikov, M. S., Ivanov, A. Y., Starova, G. L., and Khlebnikov, A. F. (2018). "Fe(II)-Catalyzed Isomerization of 5-Chloroisoxazoles to 2H-Azirine-2-carbonyl Chlorides as a Key Stage in the Synthesis of Pyrazole–Nitrogen Heterocycle Dyads." *J. Org. Chem.*, 83(6), 3177–3187.

Mironov, M. A., Maltsev, S. S., Mokrushin, V. S., and Bakulev, V. A. (2005). "A novel three-component reaction designed by the combinatorial method: Heteroarenes, isothiocyanates and isocyanides." *Mol. Divers.*, 9(1–3), 221–227.

Mishra, A., and Bäuerle, P. (2012). "Small molecule organic semiconductors on the move: Promises for future solar energy technology." *Angew. Chem. Int. Ed.*, 51(9), 2020–2067.

Moliner, F. de, Kielland, N., Lavilla, R., and Vendrell, M. (2017). "Modern Synthetic Avenues for the Preparation of Functional Fluorophores." *Angew. Chem. Int. Ed.*, 56(14), 3758–3769.

Muthusamy, S., Malarvizhi, M., and Suresh, E. (2021). "Catalyst-free synthesis of 3,1-benzoxathiin-4-ones/1,3-benzodioxin-4-ones." *Org. Biomol. Chem.*, 19(7), 1508–1513.

Nagamallu, R., Srinivasan, B., Ningappa, M. B., and Kariyappa, A. K. (2016). "Synthesis of novel coumarin appended bis(formylpyrazole) derivatives: Studies on their antimicrobial and antioxidant activities." *Bioorg. Med. Chem. Lett.*, 26(2), 690–694.

Nair, V., Deepthi, A., Ashok, D., Raveendran, A. E., and Paul, R. R. (2014). "1,4-Dipolar cycloadditions and related reactions." *Tetrahedron*, 70(19), 3085–3105.

Nair, V., Devi B, R., Pillai, A. N., and Rajan Paul, R. (2007). "A facile synthesis of thiaaza- and thiadiaza-fluorene derivatives involving benzothiazole-dmad zwitterion with arylidenemalononitriles and N-tosylimines." *Heterocycles*, 73(C), 249–254.

Nair, V., Devipriya, S., and Suresh, E. (2008). "Construction of heterocycles via 1,4-dipolar cycloaddition of quinoline–DMAD zwitterion with various dipolarophiles." *Tetrahedron*, 64(16), 3567–3577.

Nair, V., Menon, R. S., Sreekanth, A. R., Abhilash, N., and Biju, A. T. (2006). "Engaging zwitterions in carbon-carbon and carbon-nitrogen bond-forming reactions: A promising synthetic strategy." *Acc. Chem. Res.*, 39(8), 520–530.

Nair, V., Sreekanth, A. R., Biju, A. T., and Rath, N. P. (2003). "The reaction of isoquinoline and dimethyl acetylenedicarboxylate with 1,2- and 1,4-benzoquinones: a novel synthesis of spiro[1,3]oxazino[2,3-a]isoquinolines." *Tetrahedron Lett.*, 44(4), 729–732.

Nair, V., Sreekanth, A. R., Abhilash, N., Bhadbhade, M. M., and Gonnade, R. C. (2002). "A novel three-component reaction for the diastereoselective synthesis of 2H-pyrimido[2,1-a]isoquinolines via 1,4-dipolar cycloaddition." *Org. Lett.*, 4(21), 3575–3577.

Nair, V., Sreekanth, A. R., and Vinod, A. U. (2001). "Novel pyridine-catalyzed reaction of dimethyl acetylenedicarboxylate with aldehydes: Formal [2 + 2] cycloaddition leading to 2-oxo-3-benzylidinesuccinates." *Org. Lett.*, 3(22), 3495–3497.

Naskar, B., Das, K., Mondal, R. R., Maiti, D. K., Requena, A., Cerón-Carrasco, J. P., Prodhan, C., Chaudhuri, K., and Goswami, S. (2018). "A new fluorescence turn-on

chemosensor for nanomolar detection of Al^{3+} constructed from a pyridine–pyrazole system." *New J. Chem.*, 42(4), 2933–2941.

Nawaz, S., Wei, S., Huang, Y., Wang, W., Qu, J., and Wang, B. (2021). "Diastereoselective synthesis of indolenine-based spiro[pyrazolone-4,2′-pyrrolidine] scaffolds via 1,3-dipolar cycloaddition of 4-aminopyrazolones, aldehydes, and indolenines." *Org. Biomol. Chem.*, 19(32), 6964–6968.

Nayak, N., Ramprasad, J., and Dalimba, U. (2017). "Design, Synthesis, and Biological Evaluation of New 8-Trifluoromethylquinoline Containing Pyrazole-3-carboxamide Derivatives." *J. Heterocycl. Chem.*, 54(1), 171–182.

Neto, J. S. S., and Zeni, G. (2020). "Alkynes and Nitrogen Compounds: Useful Substrates for the Synthesis of Pyrazoles." *Chem. Eur. J.*, 26(37), 8175–8189.

Ngo, T. N., Ejaz, S. A., Hung, T. Q., Dang, T. T., Iqbal, J., Lecka, J., Sévigny, J., and Langer, P. (2015). "Efficient one-pot synthesis of 5-perfluoroalkylpyrazoles by cyclization of hydrazone dianions." *Org. Biomol. Chem.*, 13(30), 8277–8290.

Nicolaou, K. C., Sun, Y.-P., Peng, X.-S., Polet, D., and Chen, D. Y.-K. (2008). "Total Synthesis of (+)-Cortistatin A." *Angew. Chem. Int. Ed.*, 47(38), 7310–7313.

Nicolaou, K. C., Theodorakis, E. A., Rutjes, F. P. J. T., Tiebes, J., Sato, M., Untersteller, E., and Xiao, X. Y. (2002). "Total Synthesis of Brevetoxin B. 1. CDEFG Framework." *J. Am. Chem. Soc.*, 117(3), 1171–1172.

Orrego-Hernández, J., Cobo, J., and Portilla, J. (2019). "Synthesis, Photophysical Properties, and Metal-Ion Recognition Studies of Fluoroionophores Based on 1-(2-Pyridyl)-4-Styrylpyrazoles." *ACS Omega*, 4(15), 16689–16700.

Padwa, A., and Pearson, W. H. (2003). "Synthetic applications of 1,3-dipolar cycloaddition chemistry toward heterocycles and natural products." 940.

Panda, N., Mishra, P., and Mattan, I. (2016). "Synthesis of isocoumarins via silver(I)-mediated annulation of enol esters." *J. Org. Chem.*, 81(3), 1047–1056.

Panda, S., Pradhan, N., and Manna, D. (2018). "Ring-Opening of Indoles: An

Unconventional Route for the Transformation of Indoles to 1 H-Pyrazoles Using Lewis Acid." *ACS Comb. Sci.*, 20(10), 573–578.

Pauk, K., Zadražilová, I., Imramovský, A., Vinšová, J., Pokorná, M., Masaříková, M., Čížek, A., and Jampílek, J. (2013). "New derivatives of salicylamides: Preparation and antimicrobial activity against various bacterial species." *Bioorg. Med. Chem.*, 21(21), 6574–6581.

Peng, X., Huang, D., Wang, K. H., Wang, Y., Wang, J., Su, Y., and Hu, Y. (2017). "Synthesis of trifluoromethylated pyrazolidines by [3 + 2] cycloaddition." *Org. Biomol. Chem.*, 15(29), 6214–6222.

Poletto, J., Ribeiro, G. M., Silva, M. J. V. da, Jacomini, A. P., Basso, E. A., Back, D. F., Moura, S., and Rosa, F. A. (2019). "One-Pot Highly Regioselective Synthesis of α-Ketoamide N-Arylpyrazoles from Secondary β-Enamino Diketones." *Org. Lett.*, 21(16), 6325–6328.

Pron, A., Gawrys, P., Zagorska, M., Djurado, D., and Demadrille, R. (2010). "Electroactive materials for organic electronics: Preparation strategies, structural aspects and characterization techniques." *Chem. Soc. Rev.*, 39(7), 2577–2632.

Ali, M. R., Marella, A., Alam, M. T., Naz, R., Akhter, M., Shaquiquzzaman, M., Saha, R., Tanwar, O., Alam, M. M., and Hooda, J. (2012). "REVIEW OF BIOLOGICAL ACTIVITIES OF HYDRAZONES." *Indones. J. Pharm.*, 23(4), 193–202.

Rangasamy, M., and Palaninathan, K. (2018). "A pyrazoline-based fluorescent chemosensor for Al^{3+} ion detection and live cell imaging." *New J. Chem.*, 42(13), 10891–10897.

Redon, S., Wierzbicki, M., and Prunet, J. (2013). "A new oxa-Michael reaction and a gold-catalysed cyclisation en route to C-glycosides." *Tetrahedron Lett.*, 54(16), 2089–2092.

Reid, D. H., Skelton, F. S., and Bonthrone, W. (1964). "The addition of dimethyl acetylenedicarboxylate to thiazoles: An N.M.R. study of the structure of the adducts." *Tetrahedron Lett.*, 5(27), 1797–1802.

Reiter, M., Turner, H., and Gouverneur, V. (2006). “Intramolecular Hetero-Michael Addition of β-Hydroxyenones for the Preparation of Highly Substituted Tetrahydropyranones.” *Chem. Eur. J.*, 12(27), 7190–7203.

Rollas, S., and Küçükgüzel, S. G. (2007). “Biological Activities of Hydrazone Derivatives.” *Molecules*, 12(8), 1910–1939.

Sar, D., Bag, R., Yashmeen, A., Bag, S. S., and Punniyamurthy, T. (2015). “Synthesis of Functionalized Pyrazoles via Vanadium-Catalyzed C-N Dehydrogenative Cross-Coupling and Fluorescence Switch-On Sensing of BSA Protein.” *Org. Lett.*, 17(21), 5308–5311.

Saravana Mani, K., Rajamanikandan, R., Ravikumar, G., Vijaya Pandiyan, B., Kolandaivel, P., Ilanchelian, M., and Rajendran, S. P. (2018). “Highly Sensitive Coumarin-Pyrazolone Probe for the Detection of Cr^{3+} and the Application in Living Cells.” *ACS Omega*, 3(12), 17212–17219.

Sharma, Y. O., and Degani, M. S. (2007). “Green and mild protocol for hetero-Michael addition of sulfur and nitrogen nucleophiles in ionic liquid.” *J. Mol. Catal. A Chem.*, 277(1–2), 215–220.

Shehry, M. F. El, Ghorab, M. M., Abbas, S. Y., Fayed, E. A., Shedid, S. A., and Ammar, Y. A. (2018). “Quinoline derivatives bearing pyrazole moiety: Synthesis and biological evaluation as possible antibacterial and antifungal agents.” *Eur. J. Med. Chem.*, 143, 1463–1473.

Shi, C., Ma, C., Ma, H., Zhou, X., Cao, J., Fan, Y., and Huang, G. (2016). “Copper-catalyzed synthesis of 1,3,4-trisubstituted and 1,3,4,5-tetrasubstituted pyrazoles via [3+2] cycloadditions of hydrazones and nitroolefins.” *Tetrahedron*, 72(27–28), 4055–4058.

Shu, W. M., Zheng, K. L., Ma, J. R., Sun, H. Y., Wang, M., and Wu, A. X. (2015). “Convenient access to polyfunctional pyrazoles via a highly efficient and regioselective multicomponent reaction.” *Org. Lett.*, 17(8), 1914–1917.

Singh, S., Oyagawa, C. R. M., Macdonald, C., Grimsey, N. L., Glass, M., and Vernall,

A. J. (2019). “Chromenopyrazole-based High Affinity, Selective Fluorescent Ligands for Cannabinoid Type 2 Receptor.” *ACS Med. Chem. Lett.*, 10(2), 209–214.

Smith, L. I. (2002). “Aliphatic Diazo Compounds, Nitrones, and Structurally Analogous Compounds. Systems Capable of Undergoing 1,3-Additions.” *Chem. Rev.*, 23(2), 193–285.

Soltani, O., and Brabander, J. K. De. (2005). “Synthesis of functionalized salicylate esters and amides by photochemical acylation.” *Angew. Chem. Int. Ed.*, 44(11), 1696–1699.

Sonehara, T., Murakami, S., Yamazaki, S., and Kawatsura, M. (2017). “Iron-Catalyzed Intermolecular Hydrothiolation of Internal Alkynes with Thiosalicylic Acids, and Sequential Intramolecular Cyclization Reaction.” *Org. Lett.*, 19(16), 4299–4302.

Sustmann, R. (1971). “A simple model for substituent effects in cycloaddition reactions. I. 1,3-dipolar cycloadditions.” *Tetrahedron Lett.*, 12(29), 2717–2720.

Tang, M., Zhang, W., and Kong, Y. (2013). “DABCO-promoted synthesis of pyrazoles from tosylhydrazones and nitroalkenes.” *Org. Biomol. Chem.*, 11(37), 6250–6254.

Tang, Y., Oppenheimer, J., Song, Z., You, L., Zhang, X., and Hsung, R. P. (2006). “Strategies and approaches for constructing 1-oxadecalins.” *Tetrahedron*, 62(47), 10785–10813.

Tanini, D., Scarpelli, S., Ermini, E., and Capperucci, A. (2019). “Seleno-Michael Reaction of Stable Functionalised Alkyl Selenols: A Versatile Tool for the Synthesis of Acyclic and Cyclic Unsymmetrical Alkyl and Vinyl Selenides.” *Adv. Synth. Catal.*, 361(10), 2337–2346.

Taydakov, I. V., Akkuzina, A. A., Avetisov, R. I., Khomyakov, A. V., Saifutyarov, R. R., and Avetissov, I. C. (2016). “Effective electroluminescent materials for OLED applications based on lanthanide 1.3-diketonates bearing pyrazole moiety.” *J. Lumin.*, 177, 31–39.

Taylor, A. P., Robinson, R. P., Fobian, Y. M., Blakemore, D. C., Jones, L. H., and

Fadeyi, O. (2016). “Modern advances in heterocyclic chemistry in drug discovery.” *Org. Biomol. Chem.*, 14(28), 6611–6637.

Taylor, E. C., and Hartke, K. S. (2002). “The Reaction of Malononitrile with Substituted Hydrazines: New Routes to 4-Aminopyrazolo[3,4-d]pyrimidines1,2.” *J. Am. Chem. Soc.*, 81(10), 2456–2464.

Terzidis, M. A., Stephanidou-Stephanatou, J., and Tsoleridis, C. A. (2009). “Engaging a thiazole-DMAD zwitterion in novel one-pot multicomponent reactions involving chromones. Expeditious synthesis of thiazolo- and chromenothiazolopyridines.” *Tetrahedron Lett.*, 50(11), 1196–1198.

Thombal, R. S., and Lee, Y. R. (2018). “Synergistic Indium and Silver Dual Catalysis: A Regioselective [2 + 2 + 1]-Oxidative N-Annulation Approach for the Diverse and Polyfunctionalized N-Arylpyrazoles.” *Org. Lett.*, 20(15), 4681–4685.

Tietze, L. F., Bell, H. P., and Chandrasekhar, S. (2003). “Natural Product Hybrids as New Leads for Drug Discovery.” *Angew. Chem. Int. Ed.*, 42(34), 3996–4028.

Tron, G. C., Pirali, T., Billington, R. A., Canonico, P. L., Sorba, G., and Genazzani, A. A. (2008). “ChemInform Abstract: Click Chemistry Reactions in Medicinal Chemistry: Applications of the 1,3-Dipolar Cycloaddition Between Azides and Alkynes.” *ChemInform*, 39(24).

Turkan, F., Cetin, A., Taslimi, P., and Gulçin, İ. (2018). “Some pyrazoles derivatives: Potent carbonic anhydrase, α-glycosidase, and cholinesterase enzymes inhibitors.” *Arch. Pharm.*, 351(10), 1800200.

Veeramani, V., Muthuraja, P., Prakash, S., Senthil Kumar, M., Susaimanickam, A., and Manisankar, P. (2018). “NbCl5-Catalyzed One-Pot Four Component Synthesis of Spiro Pyrazole and Benzo[7, 8]chromene Derivatives.” *ChemistrySelect*, 3(35), 10027–10031.

Verma, D., Mobin, S., and Namboothiri, I. N. N. (2011). “Highly selective synthesis of pyrazole and spiropyrazoline phosphonates via base-assisted reaction of the Bestmann-Ohira reagent with enones.” *J. Org. Chem.*, 76(11), 4764–4770.

Vicario, J. L., Badía, D., and Carrillo, L. (2007). “Organocatalytic Enantioselective Michael and Hetero-Michael Reactions.” *Synthesis.*, 2007(14), 2065–2092.

Wabnitz, T. C., Yu, J.-Q., and Spencer, J. B. (2004). “Evidence That Protons Can Be the Active Catalysts in Lewis Acid Mediated Hetero-Michael Addition Reactions.” *Chem. Eur. J.*, 10(2), 484–493.

Wales, S. M., Merisor, E. G., Adcock, H. V., Pearce, C. A., Strutt, I. R., Lewis, W., Hamza, D., and Moody, C. J. (2018). “Diastereoselective Synthesis of Highly Substituted, Amino- and Pyrrolidino-Tetrahydrofurans as Lead-Like Molecular Scaffolds.” *Chem. Eur. J.*, 24(32), 8233–8239.

Wang, H.Y., Liu, X.C., Huang, Z.-B., and Shi, D.Q. (2015). “Copper-catalyzed Cyclization of 3-Acylcoumarin Hydrazone using Air as the Oxidant: Efficient Synthesis of Pyrazole-Fused Coumarin Derivatives.” *J. Heterocycl. Chem.*, 52(2), 380–385.

Wang, K. K., Li, Y. L., Lv, Y. J., Shen, R. H., Zhao, W., and Chen, R. (2021). “1,3-Dipolar cycloaddition reactions of azomethine ylides with seven-membered cyclic N-sulfony imines access to polycyclic sulfonamides.” *Tetrahedron*, 77, 131766.

Wang, Y., Shi, W., Wu, C., Wan, L., Zhao, Y., Zhang, C., Gu, W., and Wang, S. (2021). “Pyrazole ring-containing isolongifolanone derivatives as potential CDK2 inhibitors: Evaluation of anticancer activity and investigation of action mechanism.” *Biomed. Pharmacother.*, 139, 111663.

Wen, J., Fu, Y., Zhang, R. Y., Zhang, J., Chen, S. Y., and Yu, X. Q. (2011). “A simple and efficient synthesis of pyrazoles in water.” *Tetrahedron*, 67(49), 9618–9621.

Winterfeldt, E. (1965). “Additionen an die Dreifachbindung, IV. Cyclisierungen in der Pyridinreihe.” *Chem. Ber.*, 98(11), 3537–3545.

Wipf, P., and Graham, T. H. (2005). “Synthesis and hetero-Michael addition reactions of 2-alkynyl oxazoles and oxazolines.” *Org. Biomol. Chem.*, 3(1), 31–35.

Wu, W. T., Han, Y., Sun, J., and Yan, C. G. (2020). “Diastereoselective Synthesis of

Spiro[indoline-3,7′-pyrrolo[1,2-a]azepines] via Sequential [3+2] Cycloaddition and Ring Expansion Reaction.” *Asian J. Org. Chem.*, 9(11), 1815–1819.

Xiaoyan Xu, Jun Zhang, Hongguang Xia, and Jie Wu. (2018). “C(sp^2)–H functionalization of aldehyde-derived hydrazones via a radical process.” *Org. Biomol. Chem.*, 16(8), 1227–1241.

Xie, J. W., Wang, Z., Yang, W. J., Kong, L. C., and Xu, D. C. (2009). “Efficient method for the synthesis of functionalized pyrazoles by catalyst-free one-pot tandem reaction of nitroalkenes with ethyl diazoacetate.” *Org. Biomol. Chem.*, 7(21), 4352–4354.

Xu, P., Li, W., Xie, J., and Zhu, C. (2018). “Exploration of C–H Transformations of Aldehyde Hydrazones: Radical Strategies and Beyond.” *Acc. Chem. Res.*, 51(2), 484–495.

Xu, X., Sun, R., Zhang, S., Zhang, X., and Yi, W. (2018). “Divergent Synthesis of Quinolones and Dihydroepindolidiones via Cu(I)-Catalyzed Cyclization of Anilines with Alkynes.” *Org. Lett.*, 20(7), 1893–1897.

Xu, X., Zavalij, P. Y., Hu, W., and Doyle, M. P. (2013). “Vinylogous reactivity of enol diazoacetates with donor-acceptor substituted hydrazones. Synthesis of substituted pyrazole derivatives.” *J. Org. Chem.*, 78(4), 1583–1588.

Yang, L., Okuda, F., Kobayashi, K., Nozaki, K., Tanabe, Y., Ishii, Y., and Haga, M. A. (2008). “Syntheses and phosphorescent properties of blue emissive iridium complexes with tridentate pyrazolyl ligands.” *Inorg. Chem.*, 47(16), 7154–7165.

Yang, X., and Birman, V. B. (2009). “Acyl transfer catalysis with 1,2,4-Triazole anion.” *Org. Lett.*, 11(7), 1499–1502.

Yao, H., Song, L., and Tong, R. (2014). “Total synthesis of aculeatin A via double intramolecular oxa-michael addition of secondary/tertiary alcohols.” *J. Org. Chem.*, 79(3), 1498–1504.

Yin, Y., Hu, J. Q., Wu, X., Sha, S., Wang, S. F., Qiao, F., Song, Z. C., and Zhu, H. L. (2019). “Design, synthesis and biological evaluation of novel chromeno[4,3-c]pyrazol-

4(2H)-one derivates containing sulfonamido as potential PI3Kα inhibitors." *Bioorg. Med. Chem.*, 27(11), 2261–2267.

Yoshino, T., Sato, I., and Hirama, M. (2012). "Total synthesis of aspercyclides a and b via intramolecular oxidative diaryl ether formation." *Org. Lett.*, 14(16), 4290–4292.

Yuan, Z.-L., Wei, Y., and Shi, M. (2010). "Aza-Michael Addition Reactions of Hydrazones with Activated Alkynes Catalyzed by Nitrogen-Containing Organic Bases." *Eur. J. Org. Chem.*, 2010(21), 4088–4097.

Zhang, H., Cai, L. Y., Tang, Z., Fan, X. Z., Wu, H. H., Bi, X. F., and Zhao, H. W. (2021). "1,3-Dipolar [3+3] Cycloaddition of 1,4-Benzodiazepinone-Based Nitrones with a-Halohydroxamates for Diastereoselective Synthesis of Novel d -Edge Heterocycle-Fused 1,4-Benzodiazepinones." *Synlett*, 32(19), 1974–1980.

Zhang, Q., Meng, L.-G., Wang, K., and Wang, L. (2015). "nBu3P-Catalyzed Desulfonylative [3 + 2] Cycloadditions of Allylic Carbonates with Arylazosulfones to Pyrazole Derivatives." *Org. Lett.*, 17(4), 872–875.

Zhang, X., Kang, J., Niu, P., Wu, J., Yu, W., and Chang, J. (2014). "I_2-mediated oxidative C-N bond formation for metal-free one-pot synthesis of di-, tri-, and tetrasubstituted pyrazoles from α,β-unsaturated aldehydes/ketones and hydrazines." *J. Org. Chem.*, 79(21), 10170–10178.

Zhu, C., Bi, B., Yao, D., Chen, Q. Y., and Luo, Z. Bin. (2015). "Catalyst-Free and Oxidant-Free Synthesis of 1,3,5-Trisubstituted Pyrazoles by Michael-Type Addition of Hydrazone sp^2 Nitrogen Atoms to Enones." *Synthesis.*, 47(13), 1877–1886.

Zora, M., Kivrak, A., and Yazici, C. (2011). "Synthesis of pyrazoles via electrophilic cyclization." *J. Org. Chem.*, 76(16), 6726–6742.

Zou, Y., Hu, Y., Liu, H., and Shi, D. (2012). "Rapid and efficient ultrasound-assisted method for the combinatorial synthesis of spiro[indoline-3,4′-pyrano[2,3-c]pyrazole] derivatives." *ACS Comb. Sci.*, 14(1), 38–43.

LIST OF PUBLICATIONS

Papers Published in Peer-Reviewed International Journals

Bhaskaran, R. P., Nayak, K. H., and Babu, B. P. (2021). "Synthesis of functionalized benzo[1,3]dioxin-4-ones from salicylic acid and acetylenic esters and their direct amidation." *RSC Adv.*, 11(40), 24570–24574.

Bhaskaran, R. P., Janardhanan, J. C., and Babu, B. P. (2020). "Metal-Free Synthesis of Pyrazoles and Chromenopyrazoles from Hydrazones and Acetylenic Esters." *ChemistrySelect*, 5(16), 4822–4825.

Bhaskaran, R. P., and Babu, B. P. (2020). "Progress in Electrochemical Trifluoromethylation Reactions." *Adv. Synth. Catal.*, 362(23), 5219-5237.

Janardhanan, J. C., **Bhaskaran, R. P.,** Praveen, V. K., Manoj, N., and Babu, B. P. (2020). "Transition-Metal-Catalyzed Syntheses of Indazoles." *Asian J. Org. Chem.*, 9(10), 1410–1431.

Janardhanan, J. C., James, K., Puthuvakkal, A., **Bhaskaran, R. P.,** Suresh, C. H., Praveen, V. K., Manoj, N., and Babu, B. P. (2019). "Synthesis of hybrid polycycles containing fused hydroxy benzofuran and 1H-indazoles via a domino cyclization reaction." *New J. Chem.*, 43(25), 10166–10175.

Bhaskaran, R. P., and Babu, B. P. (2021). "Green Chemistry of Recoverable Catalysts", 299 - 322. Book chapter in *Green Organic Reactions* : Springer. ISBN: 978-981-336-897-2. DOI: 10.1007/978-981-33-6897-2.

Bhaskaran, R. P., and Babu, B. P. (2022). "*The reaction between aldehyde hydrazones and activated olefins: Metal-free synthesis to functionalized pyrazoles"* – (Manuscript to be communicated)

CONFERENCES ATTENDED

Rasmi Bhaskaran P, Megha Murali, and Beneesh P.B. (2018). "Synthesis of Polysubstituted Pyrazole via Transient zwitterion based multicomponent reactions." International Conference on Material Science and Technology (ICMST-2018), held at Indian Institute of Space Science and Technology (IIST), Trivandrum on 10-13th October, 2018.

Rasmi Bhaskaran P, Sandeep Nayak, Vibhav Damodar and Beneesh P. B. (2018). "Palladium Catalysed Aerobic Oxidative Benzoxylation of Olefins through Biomimetic Approach." 37th Annual Conference of Indian Council of Chemists (ICC-2018), held at NationalInstitute of Technology Karnataka, Surathkal, on 12-14th December, 2018.

Rasmi Bhaskaran P and Beneesh P. B. (2020). "Metal- Free Synthesis of Pyrazoles and Chromenopyrazoles from Hydrazones and Acetylenic Esters." Oral presentation (Online mode), "Neoteric Advances in Chemical Sciences (NACS-2020), held at University of Kerala, Kariavattom Campus, Thiruvananthapuram on 17-19th December, 2020.

BIODATA

RASMI BHASKARAN P

Puthiya veettil, Aduthila East, Payangadi (P.O), Kannur (Dist.), Kerala, INDIA| +91-9605417499| rasmibhaskaranp93@gmail.com

---

Personal details

Date of birth: 14.11.1993 | Gender: Female | Nationality: Indian

Education

Research Student | Department of Chemistry, National Institute of Technology Karnataka (NITK), India | Since July. 2016

Research Supervisor: Dr. Beneesh P. B.

Topic: Facile synthetic routes to functionalized nitrogen and oxygen heterocycles via zwitterion annulations

M.Sc. Chemistry | 2014-16 | National Institute of Technology Karnataka, Surathkal, India

CGPA: 9.44 out of 10, First Rank with Gold Medal

B.Sc. Chemistry | 2011-2014 | Payyanur College, Payyanur, Kannur University, India

CGPA: 3.66 out of 4, First Class with distinction

XIIth standard | 2011 | Govt. Higher Secondary School for Boys Madayi, Kerala Higher Secondary Examination Board

Percentage: 93%, First Class with Distinction

Xth standard | 2009 | Govt. Girl's Higher Secondary School Madayi, The Kerala Board of Public Examinations

Percentage: 95%, First Class with distinction

Research Publications

- **Bhaskaran, R. P.,** Nayak, K. H., and Babu, B. P. (2021). "Synthesis of functionalized benzo[1,3]dioxin-4-ones from salicylic acid and acetylenic esters and their direct amidation." *RSC Adv.*, 11(40), 24570–24574.
- **Bhaskaran, R. P.,** Janardhanan, J. C., and Babu, B. P. (2020). "Metal-Free Synthesis of Pyrazoles and Chromenopyrazoles from Hydrazones and Acetylenic Esters." *ChemistrySelect*, 5(16), 4822–4825.
- **Bhaskaran, R. P.,** and Babu, B. P. (2020). "Progress in Electrochemical Trifluoromethylation Reactions." *Adv. Synth. Catal.*, 362(23), 5219-5237.
- Janardhanan, J. C., **Bhaskaran, R. P.,** Praveen, V. K., Manoj, N., and Babu, B. P. (2020). "Transition-Metal-Catalyzed Syntheses of Indazoles." *Asian J. Org. Chem.*, 9(10), 1410–1431.
- Janardhanan, J. C., James, K., Puthuvakkal, A., **Bhaskaran, R. P.,** Suresh, C. H., Praveen, V. K., Manoj, N., and Babu, B. P. (2019). "Synthesis of hybrid polycycles containing fused hydroxy benzofuran and 1H-indazoles via a domino cyclization reaction." *New J. Chem.*, 43(25), 10166–10175.
- **Bhaskaran, R. P.,** and Babu, B. P. (2021). "Green Chemistry of Recoverable Catalysts", 299 - 322. Book chapter in *Green Organic Reactions* : Springer. ISBN: 978-981-336-897-2. DOI: 10.1007/978-981-33-6897-2.